The American Journal of Medicine

November 1947

Symposium on Allergy

Guest Editors

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and FRANCIS M. RACKEMANN, M.D.

THE YORKE PUBLISHING COMPANY, INC.

49 WEST 45TH STREET · NEW YORK 19, N. Y.

The American Journal of Medicine

The American Journal of Medicine is published monthly by The Yorke Publishing Co., Inc., 49 West 45th Street, New York 19, N. Y. Yearly Subscription, $10.00 U. S. A.; $12.00 Canada and Pan American Union; $15.00 Foreign. Single Numbers $2.00; Special Numbers $4.00. Entered as Second Class Matter June 28, 1946, at the Post Office, New York, N. Y., and at June 28, 1946, at York, Pa., under the act of March 3, 1879. November, 1947—Volume III, No. 5.

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The American Journal of Medicine

VOL. III NOVEMBER, 1947 No. 5

SYMPOSIUM ON ALLERGY

Dr. Cooke and Dr. Rackemann have designed this symposium to meet the needs of a general medical audience for a broad introduction to modern concepts of allergy. The contributors, all especially qualified by training and experience to speak with insight and authority in their respective fields, have treated their subjects critically and constructively. The whole makes an impressive, well integrated presentation.

The substance of the symposium proves the point of Dr. Cooke's introductory remarks. There can be no doubt that an intelligent appreciation of allergic mechanisms and phenomena is essential to the understanding of many of the problems of general medical practice.

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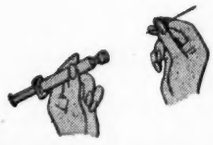

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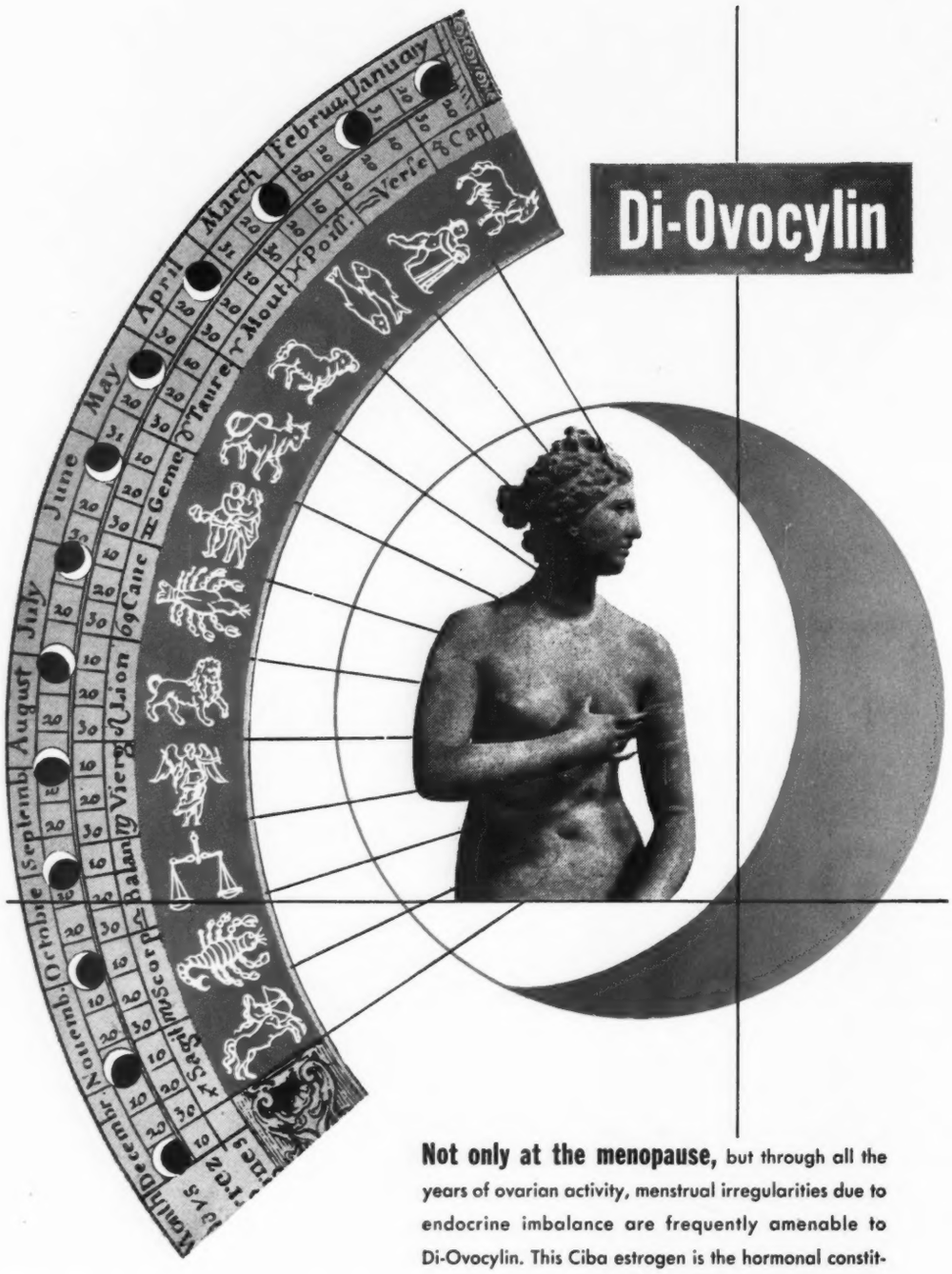

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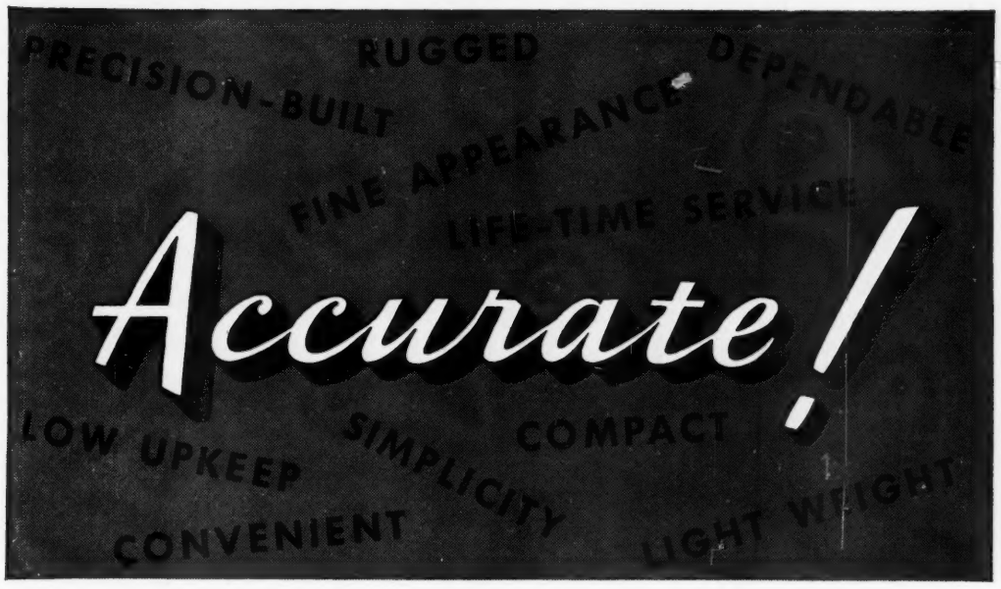

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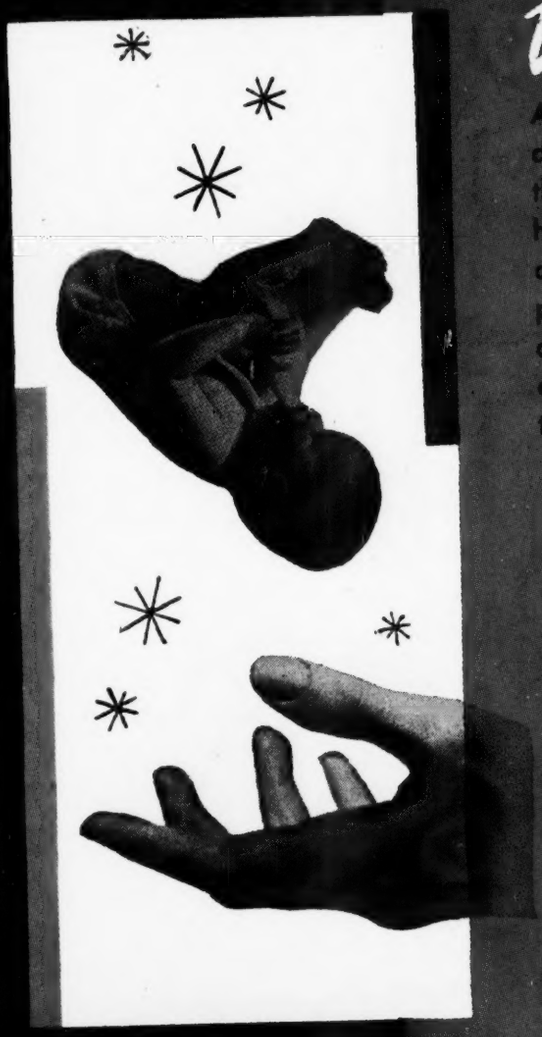

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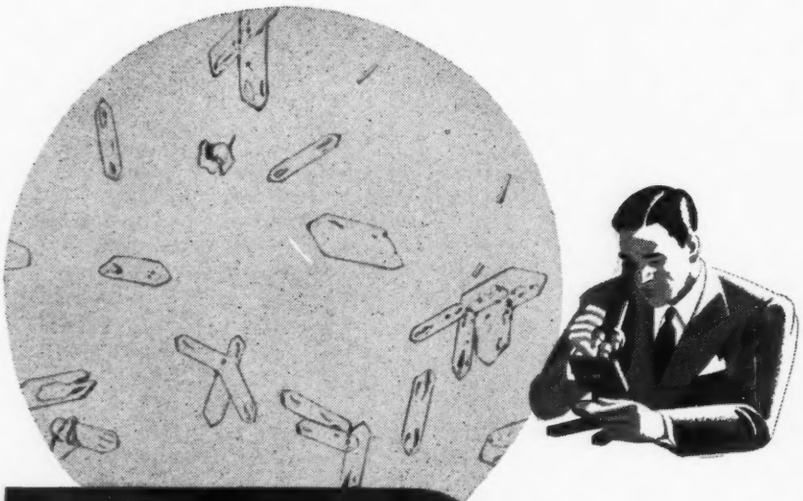

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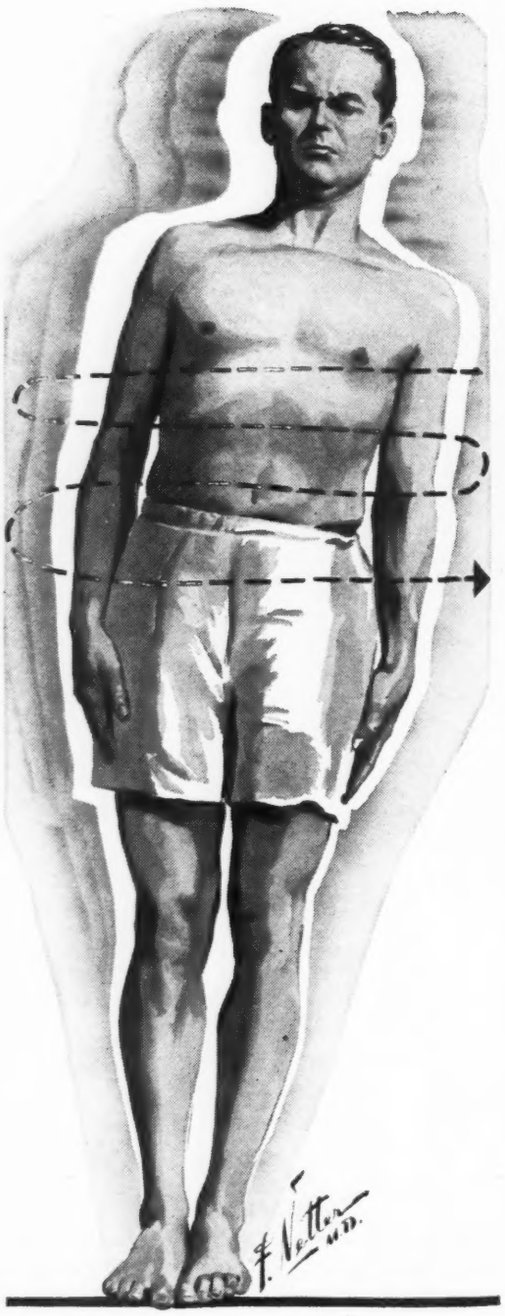

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The American Journal of Medicine

VOL. III NOVEMBER, 1947 No. 5

Editorial

Allergy Comes of Age

WHEN discoveries in science open up new avenues of approach to old problems in unrelated as well as in related fields, the usual tendency is to hurriedly attempt application if there is any suggestion of practicability, to build on theories as though they were fact, to stress the particular technics employed and to enlarge the vocabulary with newly coined words of limited and special significance. This frequently leads to an unfortunate isolation of the subject, which suffers at the hands of enthusiasts until further study and wiser minds develop the germ of truth, if there be any, and discover that the underlying principles based on fact actually are in harmony with those in other fields and that the new principles complement rather than oppose the old or exist independently of them. Of no field is this more true than of allergy which was opened up as the direct result of the discovery of anaphylaxis, in its turn a by-product of von Behring's diphtheria antitoxic serum therapy.

Not many years ago allergy was the neglected stepchild of the medical profession. To most physicians allergy merely indicated a few common but not vitally important diseases—hay fever, asthma, urticaria—and the allergist was regarded merely as a technician who did skin tests, the more extensive the better, which he assumed were a sort of diagnostic Rosetta stone. Unfortunately, this too frequently was warranted.

Gradually but steadily the situation for allergy has improved. It is emerging from its adolescence, a period quite common to most new fields of science, because careful study on the part of many has brought new knowledge which evidences the basic soundness of its concepts. Today allergy stands at the threshold of real development, for the broader vision of many minds has served to extend its horizons and increase its applicability to the possible solution of many medical problems.

It is interesting to note the extent in recent years to which allergy has come to engage the attention of those in the basic sciences of medicine, biochemistry, immunology and immunochemistry, pathology and pharmacology, as well as those immediately concerned with clinical problems, the internist, the pediatrician and others engaged in specialty fields. As proof that this is so, one need only read the contributions in this symposium dealing with pathology, immunochemistry, applied immunology and pharmacology, as well as those which concern themselves with such clinical phases as the important drug allergies, allergic dermatitis and the neuropathies, asthma and the relation of the psychic to the somatic manifestations of allergic disease. Allergy has shed its swaddling clothes and its immaturity and must be reckoned with.

A question of more than minor concern is, what are the medical schools doing for the undergraduate, and the hospitals for their interns and residents, in a field which requires their attention but to which they have had little or no introduction? A recent survey of undergraduate allergy instruction in

Class A medical schools in the United States shows a rather deplorable lack of facilities, perhaps it would be more accurate to say a failure to utilize existing opportunities for teaching the principles of allergy and providing a degree of clinical experience for the medical student. The responsibility for this must rest with the heads of departments who either fail to grasp the significance of allergy in relation to medicine, and this is certainly true of some, or, as is more probable, who cannot find time for an organized course in an already crowded schedule. That something should be done is evidenced by the complete unfamiliarity of recently graduated physicians, interns and general practitioners with the rudiments of a subject which they are promptly called upon to use.

Anyone cognizant of the recent developments in allergy and the increasing applicability of the concepts of allergy to problems in internal medicine and pediatrics must admit that it is an integral part of the basic medical sciences, bacteriology, immunology, pathology, pharmacology, physiology and clinical medicine. Bacteriology cannot be taught as it was a generation ago without reference to the tuberculin-type response of man to bacterial substances, the implications of this response, and the general relation of sensitivity to immunity. The course in immunology would be sterile without a consideration of experimental sensitization and such special technics as passive transfer, the Schultz-Dale and precipitin tests and transfer to normal human skin; this leads naturally to consideration of artificial sensitization of man to heterologous serum, serum disease and the subsequent allergic state which may be recognized by cutaneous and ophthalmic tests. In pathology the histologic responses are not to be understood without consideration of the underlying reasons for such tissue changes as the Aschoff bodies, periarteritis and fibrinoid degeneration, all of which introduce allergy as one of the possible factors in human diseases. Pharmacology cannot be adequately taught without inclusion of the increasingly important subjects of drug allergies and the antihistaminic drugs and the reasons why they have come into being.

So it is throughout all the basic courses, the fundamentals of allergy are part and parcel of them, and but little time is required to point out their future clinical applicability so that the student may approach his clinical years well grounded in the principles of allergy. A few lectures, three or four, early in the third year would then suffice to coordinate the theories and facts with such diseases as are considered in whole or in part to be based on sensitivity; for example, rheumatic fever, tuberculosis, syphilis, the erythema group, periarteritis, disseminated lupus and many of the dermatoses, as well as the recognized diseases of allergy—asthma, serum disease, urticaria, angio-edema and the various allergic reactions to drugs.

Graduate education will automatically improve as undergraduate instruction such as outlined is adopted and as approved residencies in allergy are made more available. With regard to the latter one point should be emphasized, namely, that no resident in allergy or in any other subspecialty and restricted field should be accepted until the basic requirements in medicine or pediatrics have been fulfilled.

In all such rapidly expanding subjects as allergy it is necessary from time to time to pause and evaluate what has been accomplished. This symposium is an attempt to do just that, to take inventory of the present information in certain of the basic sciences and specialties of clinical medicine in which allergy appears to be a factor. It is the hope of the guest editors that these contributions will serve a useful purpose in furthering education in the realm of postgraduate medicine, which is one of the aims to which the American Journal of Medicine has dedicated itself.

ROBERT A. COOKE, M.D.

Symposium on Allergy

Classification of the Histologic Reactions in Allergic Diseases*

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HISTOLOGIC changes have been described in practically every clinical and experimental state known or thought to be allergic. Whenever similar changes have been noted in diseases of unknown origin or uncertain nature, the allergic mechanism has been invoked as a possible factor; and indeed, with this as a clue, evidence of other sorts has, in some of these states, piled up to support such explanations. Implicit in this type of research and reasoning is the question of the pathognomonicity of the morphologic changes seen in allergic inflammations. It is probable, and some of the evidence to support this will be presented below, that none of the histologic lesions in allergic states can be said to be pathognomonic although several of them are highly characteristic.[1]

A second morphologic problem of considerable theoretic interest and some practical value is the classification of the numerous different lesions which have been described in allergic conditions. Classifications are notoriously subject to violent controversies which usually arise out of a misunderstanding of the nature of classification; it may therefore be well to look into just what one does when he classifies anything. *A classification is an arrangement of objects or phenomena according to a point of view.* Usually it is possible to arrange the same objects according to more than one point of view and at times one may choose from an extremely large number of viewpoints. Each of these classifications is as tenable as any of the others. For classifications cannot be "right" or "wrong"; they can only be useful or not useful. Even "good" or "bad" can be applied to them only in relation to this usefulness.

Classifications may themselves be classified. For instance, they may be grouped according to the tools employed and the methods used by the classifiers. Thus, when anatomic change is the basis, we have a pathologic classification; and when clinical signs and symptoms are employed, we have a clinical classification. Such classifications, limited to a rather narrow point of view, may be of great value for purely descriptive purposes and are often necessary first approximations to more valuable classifications. It is when a classification according to one point of view correlates with classifications according to other viewpoints that the greatest usefulness is attained.

A purely histologic classification of allergic states would be of some value, it is true, but certainly not of much clinical value. The classification herein attempted, however, shows interesting relationships to clinical and immunologic data and it is probable, therefore, that the histologic pictures observed are related to the clinical and immunologic phenomena. The reader should be warned, however, that this classification is not a division into perfect, mutually exclusive groups. The position in the scheme of several of the conditions is uncertain; others seems to belong in two categories and many, alas, are mixtures of

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several. This classification is at best, then, tentative and will no doubt require frequent revision.

PATHOGENESIS OF AN INFLAMMATION

The allergic reaction results in injury to the tissues which is followed by that wide variety of changes subsumed under the general title of "inflammatory reactions." A consideration of the elements which determine the anatomic changes seen in inflammation will serve as one basis for classification and it will also make it easier to understand why, in all probability, no pathognomonic allergic reaction can be found. Traditionally, two important factors are recognized: (1) The strength of the inflammatory stimulus and (2) the responsiveness of the host; or in Osler's parable, the "seed" and the "soil." But this is not the whole story. There are two additional factors which greatly influence the anatomy of an inflammatory lesion, namely, (3) the rate at which the reaction develops or its *velocity* and (4) the time during which it is active or its *duration*. These additional factors are influenced, it is true, by the first two and are in part the result of the interaction between stimulus and reactivity; but, however they are produced, they determine the anatomy of an inflammatory lesion. This fact has rarely been stipulated but has long been tacitly implied in such well known designations as *acute*, *subacute* and *chronic*. Beyond these, the hemorrhagic or necrotizing character of *hyper-acute* inflammations is well known.

A minimum time is necessary before an injury can produce anatomic changes detectable by presently available methods. Death may ensue so rapidly, either because the stimulus is very strong or because the reactivity of the subject is so violent, that no anatomic changes are demonstrable; or the duration of the stimulus and the response may be so brief and restitution to normal so rapid that, again, no anatomic changes may as yet have been found.

Sudden death without significant anatomic changes may occur when the exciting stimulus is apparently minor or at least with stimuli which in the great majority of persons and animals produce little or no damage. Such deaths are seen in the misnamed "status thymico-lymphaticus," in the fortunately rare hyper-reaction to small doses of drugs or after mental trauma.* Similarly, the anatomic changes observed in sudden death in anaphylactic shock are minimal, not in themselves sufficient to explain death and certainly not, in spite of repeated claims to the contrary, distinctive enough for a purely anatomic diagnosis. Certain other instances of sudden death without apparent adequate cause may be allergic.[2] In all of these, and in other similar instances, the characteristic feature is the marked hyper-responsiveness of the subject and I have proposed calling the phenomenon "Sudden Death in the Hyper-reactor State."

The number of elementary morphologic changes which enter into the anatomy of an inflammatory reaction is limited. They fall into four groups: (1) evidence of injury, (2) exudation, (3) proliferation and (4) repair.

Evidences of injury include necrosis and the accumulation of abnormal substances in cells (degeneration). They may be very slight or, as in necrotizing inflammation, they may dominate the entire picture. Exudation is the accumulation of substances from the circulating blood or lymph in the region of inflammation. To a large degree the severity of an inflammatory reaction is indicated by the complexity of the substances which accumulate (serum, plasma, leukocytes, erythrocytes); and inflammations are often classified according to the dominant element of the exudation (serous, fibrinous, purulent, hemorrhagic). Proliferation of cells, either of those originally present in the area of inflammation or of those reaching the area from the blood stream, may lead to the most characteristic

* I can well believe that it may be difficult to conceive of sudden death after mental trauma. I, too, might not believe in its existence if I had not myself seen such a case and performed the necropsy.

of all the features of "specific" inflammations. Repair is, of course, an element of all inflammations which regress but in some it characteristically accompanies the elements of active inflammation.

It seems probable, as a result of the last ten years' investigation into the chemistry and physiology of the inflammatory reaction,[3] that the initial impulse for the tissue changes is derived from substances released by the action of the injurious agent upon tissue cells, that these substances have very specific chemical structures (some of them have even been crystallized) and that the cellular phenomena which follow are orderly and depend upon the kinds and amounts of the substances elaborated. The identity of the principal substance which is produced by tissue damage and which initiates the inflammatory sequence is still disputed. Some believe it to be histamine or a "histamine-like substance." Menkin[3] claims it is different from histamine and has named it leukotaxine.

The relevance of these concepts for allergic inflammation must be immediately apparent, regardless of whether histamine is the substance concerned or whether the

TABLE I

DISEASES OF ALLERGIC AND POSSIBLY ALLERGIC ORIGIN*

Classification of Histologic Lesions	Diseases almost Certainly Allergic	Diseases Which May Have Allergic or Non-allergic Causes	Diseases in Which Allergy has been Suggested but Evidence is Inadequate
NECROTIZING:			
Tissue Selective	Arthus phenomenon Shwartzman phenomenon "Carbuncle" of kidney Diffuse cortical necrosis of kidney	Drug sensitivity Acute yellow atrophy of liver Acute pancreatic necrosis Necrotizing cholecystitis Necrotizing appendicitis	Encephalomyelitis[41,42] Demyelinizing diseases[43]
Cell Selective		Thrombocytopenic purpura Granulocytopenia Aplastic anemia	
ANAPHYLACTOID:	Anaphylaxis Serum sickness Asthma Atopic dermatitis Pneumonia caseosa (tuberculous) Rheumatic pneumonia[44]	Sudden death in the hyperreactor state Periarteritis nodosa Glomerulonephritis[45]	Disseminated lupus erythematosus Scleroderma Dermatomyositis Thrombo-angitis obliterans[46,47] Temporal arteritis[48] Loeffler's syndrome[49] Eosinophilic granuloma of bone Reiter's disease[50]
GRANULOMATOUS:			
Tuberculoid	Tuberculosis Brucellosis Tularemia Sporotrichosis Coccidioidomycosis		Histoplasmosis
Rheumatoid	Rheumatic fever Rheumatoid arthritis "Giant-cell" rheumatoid granulomas Rheumatoid scleritis Sympathetic ophthalmia[51,52]		

* References to literature only in those diseases not mentioned in the body of the paper.

antigen-antibody reaction injures tissue and elaborates leukotaxine.[4] There is certainly little in such ideas concerning the pathogenesis of allergic inflammation to lead to the expectation that the histology of a lesion so produced will always differ from other non-allergic inflammations. What is apparently characteristic of allergic inflammations is their velocity and duration and similar lesions may be the result of other than allergic stimuli if the velocity and duration are the same.

TABLE II

CORRELATION BETWEEN HISTOLOGIC CLASSES AND CLINICAL AND IMMUNOLOGIC PHENOMENA IN ALLERGIC DISEASES

	Type of Clinical Reaction	Clinical Course (Velocity)	Duration	Skin Reaction	Antibody in Serum	Specific Infection	Eosinophilia	Necrosis
NECROTIZING:	Immediate	Rapid	Short	0 or + Necrosis	0 or +	0 or +	0 or +	++++ (Diffuse)
ANAPHYLACTOID:	Immediate	Rapid	Short to moderate	Wheal type	Frequently +	0	+ to ++++	+ (Fibrinoid)
GRANULOMATOUS:								
Tuberculoid	Delayed	Variable	Short to long	Tuberculin type	0	+	0	++ (Caseous)
Rheumatoid	Delayed	Slow	Long	0	0	0	0 or +	++ (Fibrinoid)

A CLASSIFICATION OF HISTOLOGIC LESIONS IN ALLERGY

I. Necrotizing
   (*a*) Organ-selective
   (*b*) Cell-selective
II. Anaphylactoid (exudative)
III. Granulomatous
   (*a*) Tuberculoid
   (*b*) Rheumatoid

Table I lists the clinical entities which seem to fit into the above classifications, divided into three groups: Those which are almost certainly allergic, those which are sometimes allergic but may have other causes and those which have histologic similarity to allergic lesions and for which an allergic mechanism has been claimed but with no good clinical or immunologic evidence for such claims. These are obviously my own notions of how the diseases fit into such a scheme and considerable disagreement will be found in this respect.

Several important clinical and immunologic correlations are immediately apparent. The necrotizing and the exudative (anaphylactoid) lesions include all those conditions which clinically fall into the "immediate" reactions, the granulomatous lesions those which are the "delayed" reactions.[5] Not all instances which fall into the first two groups have positive skin reactions but, when such reactions occur, they are almost always of the wheal type. All the lesions of the tuberculoid granulomatous type have positive skin tests but they are of the tuberculin type. The rheumatoid group has no characteristic skin reaction. Circulating antibodies have not been identified in all instances in any of the subdivisions but almost all in which they have been identified fall into the anaphylactoid group, a very few in the necrotizing and none in the granulomatous.* There are differences in the necrosis in tuberculoid and rheumatoid reactions; there is also the striking fact that in the first of these a living agent (bacterium, fungus, or virus) is identifiable and

* Under very special conditions circulating antibody may be detected in tuberculosis.[6] Fundamentally, there may be no immunologic difference but for clinical purposes the difference is important.

in the second group no single organism has been implicated.

Thus it can be seen that the classification of allergic lesions according to histology has clinical and immunologic implications. These are summarized in Table II.

NECROTIZING LESIONS

Necrosis is present in some degree, usually slight or moderate, in almost all of the histologic lesions of allergy. In certain of them, however, necrosis dominates the whole picture or may even be the sole anatomic feature. The Arthus and Shwartzman phenomena of experimental allergy are such lesions and they have their counterpart in human disease.

Anatomically, the lesions are characterized by diffuse necrosis involving parenchymal cells, interstitial tissue, vascular structures and anything else in the area. (Fig. 1.) There is often a sharp boundary between areas of necrosis and normal tissue and one can imagine that the limits of the necrosis are determined by the diffusion of an antigen in a sensitized subject. Nuclear débris may be a striking feature in the necrotic zone. Around the area there is a variable amount of infiltration with inflammatory cells, usually neutrophil leukocytes. Eosinophilia is rare. In very rapidly fatal cases the peripheral cellular reaction may be entirely absent.

Several human pathologic states probably fall into this group of allergic necrotizing inflammations. Characteristic examples are the closely related conditions known as renal carbuncle and diffuse cortical necrosis of the kidney. Characteristically, these are preceded by renal infection of some kind (local sensitization) followed by a very sudden widespread necrosis of renal substance. Characteristically, too, this condition occurs as the result principally of two kinds of renal infections: Most of them are staphylococcic in origin and the remainder are usually due to pyocyaneus infections. Both of these organisms, it will be noted, produce soluble toxins.

Similar clinical and pathologic pictures of sudden onset, diffuse necrotization and little or no inflammation at the onset are seen in a variety of fairly common diseases which from time to time have been said to be allergic in origin. It is probable that the antigen-antibody reaction plays a part in some instances of these diseases but that they can be elicited by mechanisms other than the allergic reaction. Among the conditions claimed to be related to the Arthus or Shwartzman phenomena are acute pancreatic necrosis,[7] necrotizing inflammation of the appendix,[8] acute gangrenous cholecystitis and, above all, various types of drug hypersensitization. It has been claimed, for instance, that the sensitization to cinchophen is an example of the Arthus phenomenon.[9]

Now, it is here particularly, where drug hypersensitivity is being considered, that it is possible to see clearly the non-pathognomonic character of these lesions. Obviously, in cinchophen and other such hypersensitivities we are dealing with minute quantities of drugs to which most people exhibit no sensitivity and there are other evidences for the assumption of an allergic mechanism.[9] Exactly similar lesions, however, can be produced by other drugs without any evidence of previous sensitivity. Thus, the necrosis of the liver, which is thought to be an Arthus phenomenon in cinchophen poisoning, is certainly a primary degeneration in chloroform, mushroom, arsenic or phosphorous poisoning. Primary necrosis of tissues may also result from vitamin deficiencies.[40]

A phenomenon worthy of note in considering necrotizing inflammations due to drugs is organ specificity. Thus, cinchophen affects the liver but only rarely other organs, such as the pancreas.[11] Organ selectivity is, of course, even better known with primary destruction by chemical substances.[10]

The specificity of a chemical substance, however, may not be for a large organ but for a particular type of cell. Thus, following the use of gold, arsphenamine and especially sedormid,[12] many cases of thrombo-

cytopenic purpura were reported. The question of hypersensitivity in such instances and the relation of this hypersensitive state to a possible antigen-antibody reaction may be disregarded at this point in the discussion. It is important to remember, however, that similar destruction of blood platelets and production of purpuric states is well known as a result of protein hypersensitization and the antigen-antibody reaction.[13] Similarly, leukopenic states may be the result of either drug hypersensitivity or protein hypersensitivity. Although in these conditions no actual necrosis may be demonstrated histologically, it is assumed that the antigen-antibody reaction destroys the individual cells wherever they occur or at their site of origin. In favor of this view is the recently reported experimental work of Squier and Lee[14] who were actually able to demonstrate the progressive destruction of leukocytes *in vitro*. The high degree of antigen-antibody selectivity and specificity is well known in the allergic states but the high degree of organ or even cytologic specificity of these reactions requires much more study.

ANAPHYLACTOID ALLERGIC LESIONS

This group of lesions is characterized clinically by quick onset, relatively short course and often equally rapid regression, that is, by the "immediate" reactions of allergy. It is characterized pathologically by predominantly exudative changes: edema, swelling of collagen fibrils and in some cases degeneration and fibrinoid necrosis of collagen. The diseases which make up the bulk of an allergist's practice fall into this group as well as some interesting conditions whose position as allergic is equivocal.

Many of the anaphylactoid lesions are at a *presto* tempo, sudden in onset and short in duration. There is not time for anatomic change other than edema and the tissues are soon restored to a normal state. The edema may be seen grossly but in cases of acute edema it may not easily be demonstrable under the microscope since the technical methods employed by the histologist, such as fixation, sectioning and especially dehydration, cause the tissues to shrink and revert to their pre-edematous appearance. It must be noted that this histologic simplicity has no relation to clinical severity; for in these edematous lesions one may include both simple urticaria on the one hand and fatal angioneurotic edema and anaphylaxis on the other, in all of which the anatomic findings are simply those of increased fluid at the site of the lesion.

A relatively simple lesion of this group (allergic coryza) is illustrated in Figure 2. The lesion is not fresh for the edema is chronic and the tissues did not shrink in the dehydrating process but essentially the lesion presents only edema, with a few inflammatory cells, some of them eosinophil leukocytes.

If the allergic insult be repeated often enough, restitution may not be entirely to normal and anatomic changes may be encountered which are the beginning of the *secondary* phenomena observed in allergic states. Here, no doubt, is the explanation for such frequently described lesions as "hypertrophy of muscles and vessel walls," "thickening of basement membrane" and others. Many of the changes in the skin of allergic dermatoses are secondary and non-specific.

The cellular exudation varies in degree and kind. Thus, in very acute lesions the only cells present may be neutrophil leukocytes and these may be very numerous. In other more chronic lesions large phagocytic cells, i.e., monocytes or histiocytes, may be numerous or even predominate.

There is a tendency for all of these lesions, from the most acute to the most chronic, to contain a number of eosinophil leukocytes. So common is this phenomenon that eosinophilia has perhaps been overemphasized in the diagnosis of allergic histologic lesions; and the presence of eosinophilia has, from time to time led to the suspicion, for no other reason than the eosinophilia itself, that the disease may be allergic. For example, eosinophilic granu-

loma of the bone has recently been considered as possibly allergic in origin.[15]

I have discussed elsewhere at some length[1] the problem of eosinophilia in allergic and non-allergic diseases and will therefore limit this discussion to a statement of conclusions. Tissue eosinophilia is a highly characteristic finding in allergic lesions of the anaphylactoid type but it is not pathognomonic. It is highly characteristic for some non-allergic states (Hodgkin's disease, for instance) and is common in a wide variety of lesions. Furthermore, the absence of eosinophilia from a lesion does not necessarily mean that it is not allergic.

The necrosis which occurs in anaphylactoid lesions differs from that of both the predominantly necrotizing and the granulomatous lesions. In most instances it affects collagen and exhibits staining reactions resembling that of fibrin, hence *fibrinoid necrosis*. The distribution is focal and the foci are usually small and sharply delimited. Thus, in periarteritis nodosa (Fig. 3) only a segment of the wall of an arteriole may be involved while the remainder of the wall is intact.

Fibrinoid necrosis is a characteristic finding in periarteritis nodosa, so much so that one of the many synonyms of the disease is "necrotizing arteritis." The evidence is good that periarteritis nodosa may be the result of allergic mechanisms.[16] It is almost inevitable, therefore, that other diseases which exhibit fibrinoid necrosis should be considered as possibly allergic. Thus, disseminated lupus erythematosus and dermatomyositis, both of which are collagen diseases[17] with marked fibrinoid changes and both of which may be associated with periarteritis nodosa-like lesions,[18] have been considered allergic. There is no conclusive evidence that the allergic mechanism operates in these conditions, although it is entirely possible that allergy may be responsible in some instances.

Brief consideration must be given to periarteritis nodosa. The study of this disease has stimulated renewed interest in allergic mechanisms in a variety of conditions and especially in rheumatic fever and rheumatoid arthritis. Furthermore, the elucidation of the mechanisms by which it may be produced might mean that we shall have to re-evaluate certain therapeutic procedures such as serum therapy and the use of sulfonamides. The original idea that periarteritis nodosa might be allergic was based on pathologic studies[19] but the most important work has been that of Rich and his associates[16] who produced the disease by the injection of relatively large doses of foreign serum. Later[20] a relation to sulfonamide drugs was noted. Association with disease of undisputed allergic nature was found in not a few cases, especially with asthma.[21,22] Recently, association with granulomatous lesions has been reported.[23] Necrotizing arteritis has been seen in glomerulonephritis, in tuberculous meningitis[24] and, as noted above, in disseminated lupus erythematosus and in dermatomyositis. Exactly similar lesions have been produced with hormones,[25,26] carcinogens and in other ways which probably are not allergic.

Two solutions are possible for the relationship between periarteritis nodosa and allergy: The first is to accept the allergic theory and to say that all of the reported lesions are not "true" periarteritis nodosa but only resemble it. But in the absence of unequivocal etiologic criteria and with so variable and protean a clinical picture, anatomic criteria are the only criteria which can be depended upon to decide what constitutes periarteritis nodosa. For this reason the second solution seems to be the better one, namely, that anything which *looks like* periarteritis nodosa *is* periarteritis nodosa and that this condition has several perhaps many causes, one of which is allergy. This way of looking at the matter has the further advantage of the possibility of there being a common factor in all these states inclusive of allergy. One very interesting one has already been proposed by Selye[27] under the designation, "adaptation syndrome" and the "diseases of adaptation."

Rich[28] and others[29] have presented good

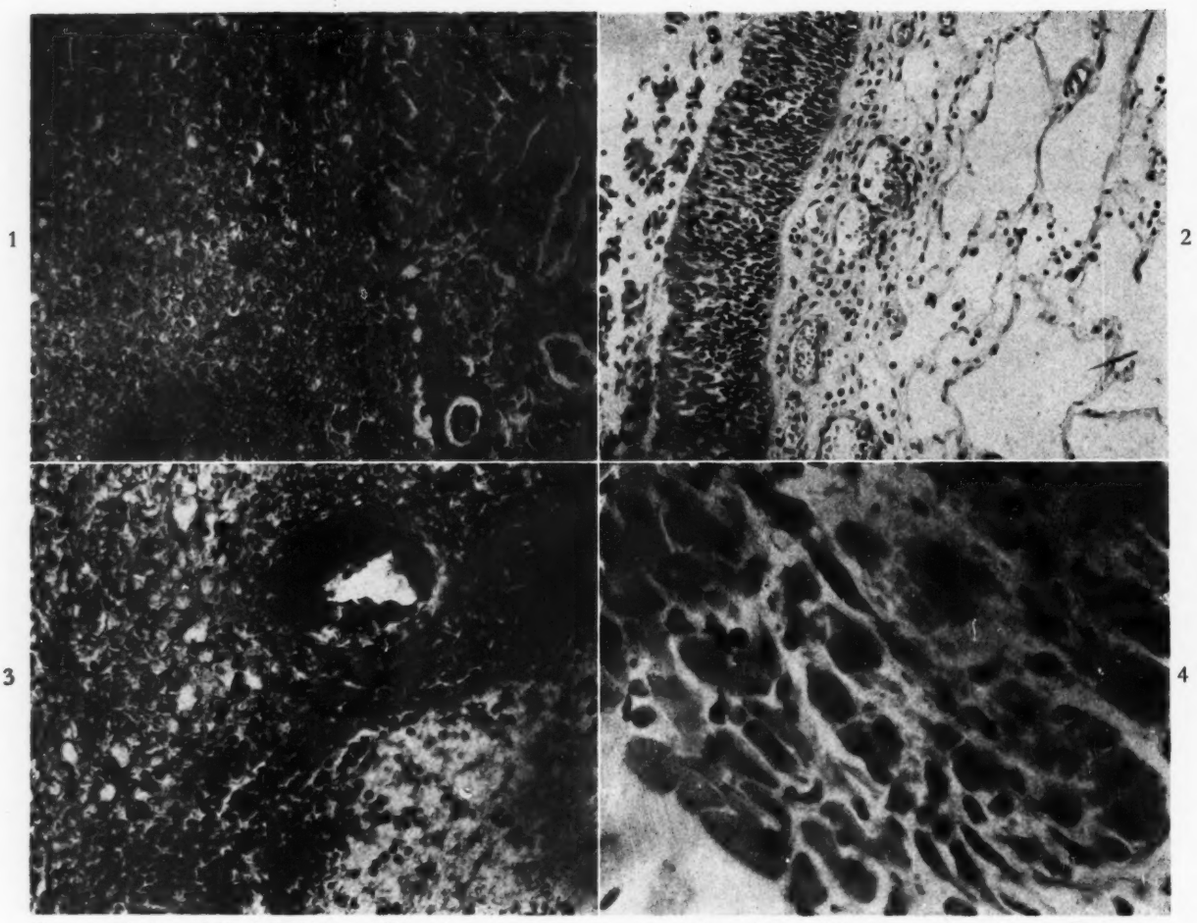

FIG. 1. "Carbuncle" of the kidney. Chronic pyocyaneus infection followed by sudden onset of renal pain. Extensive necrosis (left). Evidence of pyelonephritis in renal tubules (right).
FIG. 2. Allergic coryza. Extreme edema and hyperemia. Slight cellular infiltration. Extruded cells at left include many eosinophile leukocytes.
FIG. 3. Periarteritis nodosa. Necrotizing arteriolitis. Notice fibrinoid necrosis of only part of the wall of the vessel.
FIG. 4. Aschoff nodule, acute rheumatic myocarditis.

evidence that the Aschoff nodule in the myocardium in rheumatic fever (Fig. 4) is the result of anaphylactoid hypersensitivity. It is therefore included in this group although it shows some anatomic characteristics of the granulomatous lesions described below. The extramyocardial lesions of rheumatic fever, however, definitely belong with the granulomatous lesions.

GRANULOMATOUS ALLERGIC REACTIONS

A granuloma is a nodular, almost tumor-like structure made up of inflammatory cells which have proliferated locally. Some granulomas, including some of those we shall discuss below, are of macroscopic size which the foregoing definition intimates; but a large number of them, and certainly the units of which even the larger ones are composed, are microscopic nodules. All granulomas are the result of inflammation but not all of them are the result of infection. Thus, a very important class of granulomas is due to foreign bodies or to hemorrhage or other degenerative phenomena. The essential structure of all the allergic granulomas consists of a central area of necrosis surrounded by proliferated reticuloendothelial cells which often assume a radial, palisaded arrangement. Other features of the granulomas are variable and probably have little or no relation to the allergy. Giant cells, either of the foreign body type or of the Langhans type, may or may not be present. They may be entirely absent in tuberculosis (Fig. 5) and may be

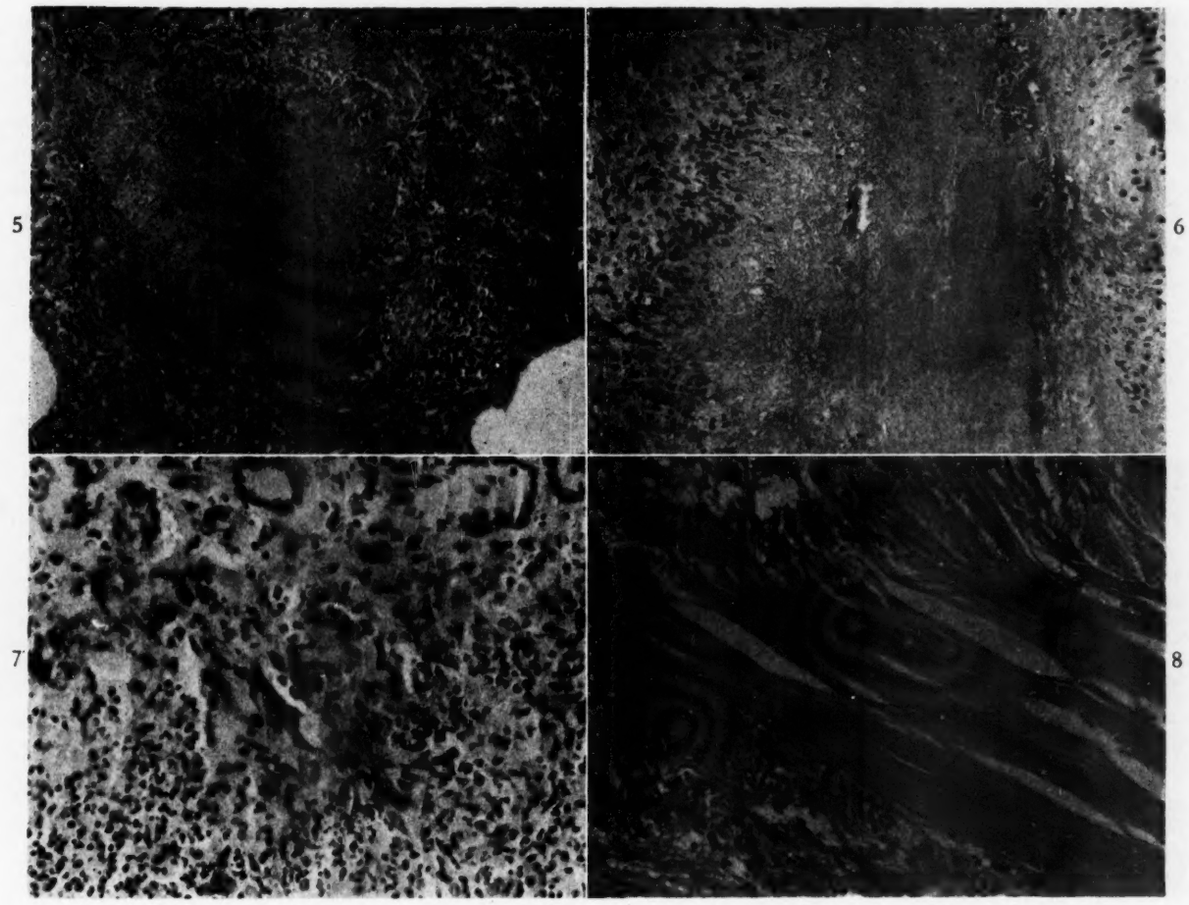

FIG. 5. Tuberculos is. Inthis case almost none of the tubercles showed giant cells. Tubercle bacilli were numerous.
FIG. 6. Rheumatoid granuloma. Skin nodule in the scalp.
FIG. 7. Granuloma in a case of periarteritis nodosa; many giant cells.
FIG. 8. Rheumatoid scleritis. Fibrinoid necrosis of the collagen surrounded by granuloma.

very numerous in non-tuberculous granulomas. (Fig. 8.) The suspicion of tuberculosis every time a giant cell is present is one of the most reliable evidences that the pathologist is an amateur. Non-allergic granulomas may have all the features of the allergic granulomas except that they lack necrosis.

In some allergic granulomas the central area of necrosis is in the proliferated inflammatory tissue and is called caseation necrosis. In others the necrosis is in pre-existing collagen and is called fibrinoid necrosis. This anatomic difference delimits two groups of granulomatous allergic lesions, the *tuberculoid* and the *rheumatoid*. It is a remarkable fact that these two groups are also differentiated by clinical phenomena: The tuberculoid granulomas are all caused by well known living agents and give positive tuberculin-like skin tests with appropriate antigens; while in the rheumatoid lesions no single living agent has been identified as the cause, (there is, indeed, reason to believe that there may be more than one cause) and no characteristic skin tests are known.

Tuberculoid Allergic Lesions. At one time the histologic diagnosis of tuberculosis was a matter of utmost simplicity. Gradually it has been recognized that there are many nodular lesions which resemble tuberculosis but are not tuberculous. On the one hand there are foreign body reactions (especially those due to silicates, including talcum granulomas) and sarcoidosis, all of which lack central necrosis. On the other hand there are infections such as brucellosis, tularemia, sporotrichosis, lymphopathia venereum and coccidioidomycosis. Tubercle

bacilli are, therefore, searched for in tissue sections today more often than they were a generation ago.

The characteristic tubercle occurs as a reaction to tubercle bacilli only after sensitization to tubercle bacilli has been established.[30] There is good reason to believe that the necrosis is entirely the result of tuberculo-protein acting in a sensitized subject. The peripheral portions of the tubercle, and particularly the giant cells and histiocytes, can be elicited by dead tubercle bacilli or by lipoid fractions of tubercle bacilli. Lipoids, it will be remembered, are the most potent single excitant for giant cell production.

One of the non-caseating tuberculoid lesions, *sarcoidosis*, deserves special mention because of its clinical relationships to tuberculosis. The histiologic lesions of sarcoid lack the necrosis of allergic granulomas; correspondingly, they almost always have a negative tuberculin skin test and therefore lack clinical evidence of tuberculo-allergy. Tubercle bacilli are rarely found in sarcoid lesions but occasionally are fairly numerous. (Fig. 5.) I have seen lesions histologically identical with sarcoid (even showing asteroid inclusions in giant cells) around foreign bodies (plant cells, talcum, lipoid accumulations). For these and other reasons I think it is probable that sarcoidosis is essentially a foreign body reaction in which non-pathogenic tubercle bacilli are commonly the exciting foreign body.*

The caseating tuberculoid lesions may all appear the same on histologic examination. They have this feature in common, that in all of them positive skin tests of the tuberculin type may be obtained. It is probable that the similarity in histologic structure is due to the similar kinds of allergic states and that the minor differences, more of statistical than of pathognomonic importance, are due to differences in the causative micro-organisms.

* I once mentioned this notion to Dr. Paul Klemperer who intimated that he held similar ideas (I hope I am not misrepresenting him) and in support he read to me a reference to the fact that non-pathogenic tubercle bacilli have higher lipoid content than pathogenic ones.

One word of caution and just one indication that the pristine simplicity of classification must not be gulped down whole. Histoplasmosis is a fungus infection in which positive tuberculin-like skin tests can be obtained with appropriate antigens (histoplasmin). Yet its histology does not even faintly resemble allergic reactions of any kind but instead consists of a simple stuffing of reticulo-endothelial cells with fungi. Does this reticulo-endothelial "blockade" alter the tissue reactions? Or is it relevant at this point to know that the specificity of the histoplasmin reaction has been questioned?

Rheumatoid Granulomas. The subcutaneous nodules, joint lesions and the less common lesions of both rheumatic fever and rheumatoid arthritis show very similar histologic structure. (Figs. 6 and 8.) The characteristic features of these lesions is the fibrinoid necrosis of *pre-existing collagen* in the centers of the granulomas. The necrosis tends to be more marked in the lesions of rheumatic fever which corresponds to the more rapid clinical course of this lesion as compared with most cases of rheumatoid arthritis. This and other minor differences in the frequency with which some parts of the granuloma occur in rheumatic fever lesions on the one hand and in rheumatoid arthritis on the other are slight and insufficient to distinguish the two on histologic grounds.[31]

There exist certain lesions whose structure is basically that of the rheumatoid granulomas but whose relation to rheumatoid lesions is still disputed. One group of these will serve as an example. Two lesions of the sclera have been described, both of them rare, which have identical histologic lesions resembling the rheumatoid granuloma. Differences in the distribution of the lesions in the sclera and certain minor clinical differences have been described in brawny scleritis[32,33] and scleromalacia perforans.[34,35] Based on the very small number of reported cases, it is said that scleromalacia perforans is regularly associated with rheumatoid arthritis, whereas brawny scleritis is usually

not so complicated. Recently we have seen an instance of this kind in which the arthritis was severe, the clinical features of both scleromalacia and brawny scleritis were present and the distribution of the lesions was that of both conditions. The essential elements of the histologic lesions were those of rheumatoid granulomas. (Fig. 8.) We believe that the similarities between these two diseases are more important than the minor differences and we propose that the two be subsumed under the single designation, "rheumatoid scleritis."[36]

More common than the eye lesions are granulomas in the respiratory tract, especially in the nose. These often contain large numbers of giant cells and have frequently been called "giant-cell granulomas." Their lethal nature has been well known.[37] Rössle[38] first identified them as accentuated forms of "rheumatism" and noted their relation to vascular lesions. They were then described as occurring in borderline forms of periarteritis nodosa[39] and finally several reports appeared[23,40] in which the granulomas and periarteritis nodosa were definitely associated. Figure 7 is from a recent case in which, after the usual misdiagnosis of tuberculosis (see the giant cells), the diagnosis of granuloma and periarteritis nodosa was made from a nasal biopsy.

In spite of the striking evidence that the lesions in this group are characteristically allergic, the absence of immunologic corroboration makes their position somewhat equivocal and their location in Table I is intended to portray this fact.

SUMMARY

An attempt to classify the histologic lesions seen in allergic diseases is herein presented. It is shown that anatomic differences in these lesions divide them into a relatively small number of groups, each of which has not only a certain histologic identity but clinical and immunologic similarities as well.

Pathognomonic significance cannot be claimed for any of the lesions described but all of them are highly characteristic and their presence *suggests* allergy as a possible cause. Many of the lesions can, no doubt, be caused by both allergic and nonallergic mechanisms.

The position of some of the diseases in this classification is uncertain and may have to be changed. It is hoped, however, that the classification may suggest considerations which will clarify these anomalous positions and lead to a more useful classification.

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The Immunology of Allergic Disease*

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IN writing on allergy, especially in its broader phases, it is still necessary for the author to interpret what he means by the word. This is more readily done by explanation than by definition. That state of well being which we call health results from the proper or normal action, reaction and/or interaction of the vital cells of the body. Disease, however, for the most part is the response of cells to an abnormal environment that is created by too much or too little of the normal products of nutrition, or of the various glandular secretions or is the result of poisons from without or within including those of invading bacteria and viruses. All of these disease-producing factors exhibit more or less widespread evidence of organic or functional disease through their *direct* effect or action, either positive or negative, on various tissue cells.

On the other hand, there is another group of agents which produce toxic effects by *indirection*. They are those substances, themselves usually harmless, which exert profound and even lethal effects upon tissue cells because of a specific sensitization. Such reactions, when mediated by an antibody mechanism, constitute allergy.

Under this broad interpretation many manifestations are encountered with varied etiology, pathology, immunology and symptomatology, affecting the cells of many tissues and organs and often having no apparent relationship. However, a common denominator which justifies the use of the word "allergy" can, I think, be found in the fact that the tissue responses are based upon the proved or reasonably assumed existence of a cellular antibody that has a specific affinity for an antigen which when present becomes linked to the sensitized cell. This causes a cellular response that is varied, depending upon the character, function or type of cell, the chemical nature of the antigen, the type of contact and the immunologic mechanism. The fact is, however, that the resultant reaction is always "altered" from that of the same substance in contact with non-sensitized cells.

This concept of allergy is somewhat at variance with the original "altered reactions" for which the word allergy was coined by Von Pirquet;[1] he was describing the quantitative variations of the anamnestic reaction rather than the qualitative changes which result from an existing sensitization and for which the word has been appropriated

As to the details of the chemistry and pharmacology of those substances which are derived from the action of antigen on sensitized cell, there is still little precise knowledge. In that immunologic reaction exemplified by animal anaphylaxis and by serum shock, studies have shown that histamine or a histamine-like substance is at least one of the toxic agents released from the cells in which it exists in a bound state. Through its pharmacologic action on cells histamine produces edema and hyperemia which are characteristic of the immediate wheal-type allergic reactions. Under appropriate conditions smooth muscle contraction also occurs. But this is about as far as one can go today. Why tuberculin produces its inflammatory effects only on those cells sensitized by a prior tuberculous infection and why the phenols of plants like poison ivy produce the irritative reaction of dermatitis only on persons previously sensitized to the plants is not known. On *a priori* grounds there must be other agents

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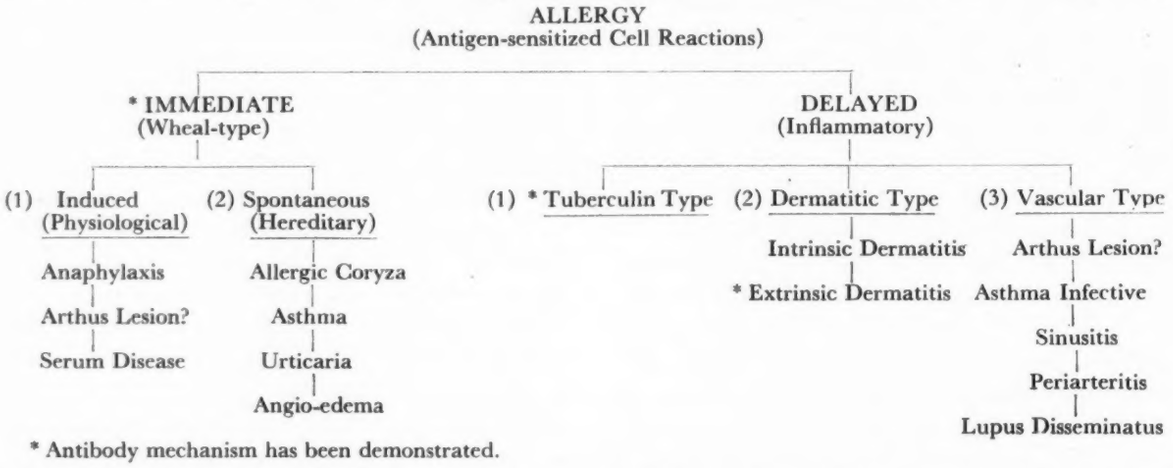
than histamine for the action upon sensitized cells of tuberculin, poison ivy and similar allergens bears no resemblance to those effects which histamine or other products of the anaphylactic reaction are able or known to produce. This thought is entirely in keeping with and analogous to that of Menkin[2] who has described the many agents in inflammatory exudates such as leucotaxin, necrosin, pyrexin and the leukocytosis promoting factor, each producing its own special effect.



* Antibody mechanism has been demonstrated.

AN IMMUNOLOGIC CLASSIFICATION

When one observes the different types of accepted antigen-antibody activity, one single fact stands out above others: Either the reactions are "immediate" (within one hour) or they are "delayed" for several days, assuming of course the pre-existence of the sensitized state; for example, the development of serum disease after the normal incubation period does not represent delayed reaction, for once antibody has been produced, the reactions of antigen on sensitized cell are prompt.

On this basis an attempt has been made to schematize the various reactions, and while such a classification as the following may not and probably will not be entirely adequate or permanent, it will serve as a framework for this immunologic discussion.

IMMEDIATE REACTIONS (WHEAL-TYPE)

As a result of the discovery of anaphylaxis, the application of its principles to certain diseases of man and the subsequent studies in the field of human allergy, it has become clear that certain types of sensitization are readily developed artificially in animal and man to such an extent that they must be regarded as normal or, as I[3] originally termed them, *physiologic* responses to antigenic stimulation. This is in marked contrast with a group of human (occasionally animal) reactions that develop spontaneously and in which an hereditary factor plays a significant rôle. As we see it today, practically all human beings are sensitized by heterologous serum (90 per cent[4]), by the phenols of ivy (70 per cent[5]), by tuberculous infection (100 per cent) and by certain drugs (nirvanol 80 to 90 per cent); whereas only a small fraction of mankind[6] (10 per cent) develop the spontaneous clinical allergies upon natural exposure to airborne and ingested allergens.

However, the hereditary factors involved in both artificial and spontaneous sensitization are extremely complex. In animals the importance of heredity was demonstrated by Webster[7] in strains of mice with high and low susceptibility to mouse typhoid infection and by Chase[8] who developed strains of guinea pigs with high and low susceptibility to sensitization (dermatitis) with simple chemicals and poison ivy. The fact is that clinical studies[6,9,10,11] in man have shown that heredity is certainly a significant factor in the spontaneous allergies of man and may likewise be a factor, though less apparent, in susceptibility to

sensitization on contact with known allergens. A recent paper by Neel[12] discusses more fully the complexity of the genetic factors involved in inherited disease. There are very considerable differences in the degree of susceptibility of man to parenteral injections of horse serum; but 10 per cent develop serum disease after small (5 to 10 ml) doses whereas with large amounts (100 ml) the symptoms occur in 90 per cent. That this susceptibility is individual and selective as well as dependent upon factors of antigenicity is indicated by the studies of Landsteiner et al.[13] and by general clinical observation.

INDUCED ALLERGIES

Animal Anaphylaxis: Since Richet's[14] work on actinia in 1902 and that of Theobald Smith[15] on diphtheria antitoxin in 1904, anaphylaxis has been extensively studied and is the basis for the concept of human allergy. When a small dose (0.1 to 1.0 ml) of horse serum is parenterally injected into a normal guinea pig, there is no observable effect. When this dose is repeated in a week or ten days or after longer intervals (up to two years), there is an immediate reaction (anaphylactic shock) with dyspnea, cough, convulsions and frequently death in a few minutes though the animal may recover.

Members of almost all of the animal kingdom appear to be susceptible to sensitization in varying degrees but the guinea pig appears to be most readily sensitized and the rhesus monkey one of the least. Regardless of the antigen used, the symptoms are the same in any one species but vary widely in different species. In the guinea pig death is due to asphyxia from bronchospasm but there is also contraction of all smooth muscle. The lungs are markedly emphysematous. In the dog there is vomiting, bloody diarrhea and collapse. The liver and abdominal organs are engorged with blood due to contraction of the muscle pads of the hepatic veins. The rabbit suffers circulatory failure with dilatation of the right side of the heart caused by spasm of the pulmonary vessels. The anaphylactic reaction in the horse is evidenced by edema and urticaria. In all animals the reaction is prompt with smooth muscle spasm and increased capillary permeability; in other words, the reaction is basically the same though symptoms vary with the species.

It was on the basis of the similarity of species reactions, regardless of the antigen, that Dale[16] suggested histamine as the long sought anaphylatoxin. There are some very sound reasons for believing that this is so, in part at least, but this has been reviewed by Feldberg[17] and by St. Went[18] and is discussed in Rose's article in this symposium. It need not be elaborated here except to state my belief that histamine can be the factor only in the *immediate* wheal-type allergies.

The antigens responsible for this induced anaphylactic sensitization are usually proteins, in some cases proteoses; but simple chemical compounds of low molecular weight in general do not act as antigens unless combined as a haptene with a protein, in which case the simple chemical may be the determinant or specifically reacting group rather than the protein. The exceptions are phthalic anhydride, producing sensitivity in man (Kern),[19] and citraconic anhydride used by Jacobs et al.[20] and Landsteiner and Chase[21] in guinea pigs.

To produce sensitization the antigens may be administered by any parenteral route; in the guinea pig sensitization has been accomplished as well by ingestion and inhalation of protein distinctly foreign to the animal. Shock is elicited by parenteral injection of antigen after an incubation period of eight to twelve days. The reactions are most striking after an intravenous dose.

That sensitivity has developed may be demonstrated in any one of several ways: (1) by anaphylactic shock; (2) by passive transfer of sensitivity, that is, if a sensitized animal is bled and its serum injected into a non-sensitive animal even of another species (e.g., rabbit to guinea pig), the latter after a short period (four hours) will show shock when injected with the original antigen;

and guinea pigs born of a sensitized mother also may be shocked by an injection of the specific antigen, thus showing placental filtration of the sensitizing antibody; (3) by *in vitro* tests, precipitation and complement fixation in the presence of antigen; (4) by the Schultz-Dale reaction, the *in vitro* contraction of smooth muscle of the uterine or intestinal strip on addition of antigen; (5) by the injection of sensitive serum (human, guinea pig or rabbit) into the skin of normal man.[22,23,24,25] Such a site tested after a few hours with the antigen may show a typical urticarial wheal.

There are then, excepting the active shock reaction, three useful tests by which antibody may be demonstrated in the serum of the sensitized animal; the precipitin test, the Schultz-Dale test for smooth muscle sensitizing antibody and the passive transfer to human skin of the skin sensitizing antibody. The evidence that these tests are dependent upon separate and distinct antibodies lies in the fact that quantitative correlation between them is not always demonstrable. One may find a high precipitin titre and low sensitivity capacity by passive transfer and vice versa. The relation of these antibodies to those found in man after serum disease and in such spontaneous allergies as asthma will be discussed later.

Another phase of animal anaphylaxis should be mentioned. *Desensitization*[26] by the injection of sublethal amounts of antigen is readily accomplished. During this time large doses of antigen may be given without the production of symptoms and an animal may be kept desensitized by frequent repeated injections of antigen. In fact, such doses may produce a state of clinical immunity even though anaphylactic antibodies are demonstrable in the serum. In short, the line between sensitization and immunity is not well defined nor is the mechanism of this immune state thoroughly understood at this time.

The *Arthus phenomenon*[27] should be mentioned in this connection. While it may occur in other species, it is produced notably in rabbits. Repeated subcutaneous injections of protein ultimately produce a local inflammatory response which may proceed to necrosis. This is due to the fact that the reaction takes place chiefly in the walls of blood vessels. It is not, therefore, an essential part of the anaphylactic reaction *per se* and confusion arises from the fact that the anaphylactic antibodies are also present as a result of the sensitizing procedures. Histologically, these reactions are more closely related to those lesions which Rich[28] has described in rabbits and man following administration of serum and sulfonamides and are closely related to, if not identical with, those of periarteritis and disseminated lupus. The immunologic mechanism of the Arthus phenomenon and of the related vascular lesions is not fully understood.

Serum Disease and Post-serum Disease Sensitization. Serum sickness is the term applied to the reaction which develops in normal man seven to twelve days after a primary injection of serum. Its incidence varies from 10 to 90 per cent and, as previously stated, is roughly proportional to the size of the dose. The main symptoms are urticarial eruption, fever, arthralgia and lymphadenitis. Occasionally, the central and peripheral nervous system is involved, presumably an edema of meninges or nerve sheath. Fatalities are practically unknown. There may be several recurrences in rapid succession, probably reactions to the different serum proteins.

Among the many immunologic studies, those of Longcope and Rackemann[29] and Mackenzie[30,31] especially have thrown light upon the mechanism underlying this disease. During the incubation period the heterologous serum may be demonstrated in the blood. With the onset of symptoms, antibodies (precipitins) appear and with their increase the foreign antigen rapidly disappears from the blood. The symptoms are caused by a reaction of the newly formed cellularly attached antibodies and the residual antigen. The symptoms disappear with the removal of antigen from the body which is then left in a state of sensitization entirely analogous to that of the anaphylac-

tic animal. This state of cellular sensitization is readily shown in man by a positive immediate wheal reaction on skin and eye test with the appropriate serum. The antibodies are also demonstrable in the serum for they will precipitate antigen *in vitro*, passively sensitize guinea pigs (Schultz-Dale) and transfer sensitivity to the skin of normal man. In man this state of reactivity is usually temporary (for weeks or months) though Mackenzie[31] has reported sensitization to serum lasting from two to eight years. Von Pirquet and Schick[32] showed that in those who had had previous injections of horse serum and lost their sensitivity, the incubation period was shortened considerably after a later injection; that is, the reaction was accelerated, a form of the anamnestic response of cells trained by previous stimulation.

In man, anaphylactic shock has occurred as in the animal when a second injection of antigen is given after a seven to twelve-day incubation period, or even weeks later, although the initial injection caused no symptoms. These cases are of course accidental and understood only in retrospect, hence have not been carefully studied. The reactions have been caused, as a rule, by secondary injections of heterologous antiserums, liver extracts, tetanus toxoid (proteose) and viral vaccines produced in egg yolk. Reference will not be made here to the shock reactions following *primary* injections for these are an evidence of spontaneous allergy and should not be included in this group.

SPONTANEOUS (HEREDITARY) ALLERGIES OF MAN

Such diseases as asthma, hay fever (both seasonal and perennial), dermatitis (infantile eczema), urticaria and angio-edema are accepted allergies in which hereditary factors have been shown to be significant. Certain patients with disturbances in the central and peripheral nervous and gastrointestinal systems, when due to foods or drugs, may also belong in this group.

The common allergens include airborne pollens, danders, mold spores, various dusts encountered at home and at work as well as foods and drugs. The reason why one individual becomes allergic to one substance and another to a different one is not known. The offspring of allergic parents inherit not a specific sensitization but the capacity or tendency to be allergic.[6] There is no placental transmission of sensitizing antibody in these spontaneous allergies of man.[33,34] Presumably, contact is a determining etiologic factor in many cases as indicated by a sensitivity to castor bean in those living near a bean-processing plant and an increasing allergy to the pollen of sugar beet which Phillips[35] showed followed the introduction of sugar beet in a restricted area. But many persons develop a high degree of sensitivity when there has been no apparent contact, as evidenced by the severe shock reactions following the first injection of horse serum which occurred not infrequently in the earlier days of treatment with diphtheria antitoxin.[36]

The pathologic reaction is one of vasodilatation and increased capillary permeability with edema which takes place in all sensitized tissues, especially skin and mucous membrane. In the latter, the reaction also stimulates mucoid secretion which is a conspicuous feature of hay fever, asthma and of reactions of this type in the intestinal tract. Such allergies are usually accompanied by an excess of eosinophilic leukocytes in the tissues, in their secretions and in the circulating blood.

Clinical Studies. The outstanding characteristic of these reactions is their promptness, both symptomatically and by test. The person who has asthma and is sensitive to cats develops the asthmatic reaction promptly, perhaps in five minutes, certainly within an hour, if adequately exposed. This may mean simply entering a home where cats are house pets. If one skin tests this person with an extract of cat dander, there is an immediate wheal-type reaction at the test site; and if one injects the serum of a cat-sensitive person into the skin of a normal person and then tests the site with

the cat dander extract, the same prompt wheal is produced. This is known as the Prausnitz-Küstner[22] phenomenon of passive transfer of sensitiveness. The point is that no matter how the skin test is done, directly or indirectly, the reactions are always immediate with wheal formation only; that is, they are temporary and completely reversible. The clinical reaction in the mucous membrane is the same immediate edema as is the skin test and the symptoms referable to the respiratory tract, both vasomotor rhinitis and asthma, are due to the reaction of the lining membrane of nose, bronchi and bronchioles. The significant point is that if a test reaction is an immediate edema the clinical reaction will also be an immediate edema in the sensitized tissue. Immunologically, histologically and clinically, the test response and the clinical reaction must be of the same kind. This is basic and pertains to all types of allergic reactions.

An allergic reaction takes place only in the sensitized cells. It is to be expected then that persons with this type of allergy, that is, of the mucous membrane of the respiratory tract, would have as causes for symptoms mainly those inhaled airborne substances such as pollens, animal emanations and dusts of various sorts and, much less frequently, ingested foods or drugs.

In addition to asthma and hay fever, the reactions of the immediate wheal-type also express themselves clinically as urticaria and angioedema reactions of skin and gastrointestinal tract, usually caused by ingested foods or drugs and very rarely by inhaled allergens.

If a person after eating fish or shell fish develops urticaria within one hour, often with associated gastrointestinal symptoms, the type of allergy concerned is identical with that found in pollen hay fever, for one quite regularly obtains a positive skin test and passive transfer of sensitivity by serum to a normal skin. Patients with such immediate reactions to certain foods usually relate cause and effect and abstain from their use. They rarely need a physician to confirm a diagnosis they have made for themselves. It is in this form of allergy and in this alone that the wheal-type of skin test is useful in determining or confirming a specific cause.

However, there are edema reactions that appear to be exceptions to this rule. Many patients with urticaria and angio-edema do seek medical aid because they cannot relate cause and effect for themselves since the clinical response is not immediate but may be delayed for four to twenty-four hours or more. These reactions, originally described by Cooke,[37] are important because they are common, especially in patients with symptoms referable to viscera and to the central nervous system and because the usual diagnostic approach with skin tests is of no avail. The explanation for certain of these cases is afforded by studies reported by me[38] a few years ago and confirmed by Blamoutier.[39] One of the patients then described illustrates the point. He had abdominal pain and diarrhea four to five hours after ingestion of milk. Once the allergen was determined, the attack was regularly reproduced and always after the specified incubation period of four to five hours. The skin test with whole milk was negative but it was positive with a proteose fraction of milk. The delayed appearance of the reaction is explained by the fact that it takes about four hours for the patient to digest milk to the stage in which it becomes allergenic. Immunologically, it is the same immediate wheal reaction but clinically it has the appearance of a delayed reaction. These cases are difficult diagnostic problems. The fixed incubation period is the clinical criterion for it remains the same in the particular patient for the particular food.

Serologic Studies. The Skin-sensitizing Antibody: When one studies the serum of untreated patients with spontaneous allergy of the immediate wheal-type, such as hay fever, using the various laboratory technics as applied in the work on anaphylaxis and serum disease, interesting characteristics appear.[40] No precipitate has yet been shown by the addition of antigen to the serum *in*

vitro and there is no demonstrable combination of antigen with the antibody *in vitro*. Presumably it can combine only after the antibody has become cellularly attached when a wheal reaction will ensue. When the serum is injected into guinea pigs, they are not sensitized passively, that is, they cannot later be shocked, neither is the Schultz-Dale reaction positive; in other words, there is no evidence of an antibody that will sensitize smooth muscle and produce bronchospasm or uterine contraction. Such serum injected into rhesus monkeys will sensitize the skin and mucous membrane and give immediate wheal reactions to antigen, as shown by Straus,[41] but there has been no evidence of any smooth muscle response. When this sensitive serum is injected intradermally into a normal man, the site will respond specifically when tested with the antigen a few hours later. The response is an immediate wheal and the site is readily desensitized. When sensitive serum is injected intravenously a general sensitivity may result with a clinical response (asthma), as reported by Ramirez[42] who cites a patient with pernicious anemia transfused with blood of an asthmatic allergic to horse dander. This work has been confirmed by Loveless.[43] Such passive sensitivity is temporary, for days or weeks only.

The skin-sensitizing antibody exists in the serum of the spontaneously allergic person in large amounts for serum diluted several thousand times may still give positive reactions on transfer to the skin of normal test-subjects.[40] This antibody does not pass the human placenta[33,34] for it is not found in cord blood. An interesting characteristic of this antibody is that it does not carry a high degree of specificity, nothing comparable to that of artificially produced precipitins, as shown by direct tests or by cross-neutralization experiments.[40] It is destroyed by heating the serum at 56°c. for four hours[44] and in this way differs from the artificially produced blocking antibody to be described.

In summary, then, the skin-sensitizing antibody in the spontaneously sensitive man has never yet been proved to act as a precipitin and cannot sensitize smooth muscle but has an affinity for cells of skin and mucous membrane. There is no evidence that it can combine with antigen except in these cells. It is spoken of as a skin-sensitizing antibody and has been referred to at times as reagin.

Cooke and Spain,[23] using precipitin (Schultz-Dale) and passive transfer tests, made comparative serologic studies, later confirmed, of rabbits sensitized to horse serum (anaphylaxis), of man after serum disease from antitoxin and of an asthmatic spontaneously sensitive to horse serum. The significant differences that appeared may be tabulated as follows, the average extent of reactions being indicated by the number of plus (+) signs:

	Precipitin	Smooth Muscle (Schultz-Dale)	Passive Transfer to Human Skin
Artificially sensitized animal (anaphylaxis)	+++	+++	+
Artificially sensitized man (serum disease)	+++	+++	+++
Spontaneously sensitized man (asthma)	0	0	++++

These studies, abundantly confirmed, show that the antibody that sensitizes the skin of the naturally sensitive man (asthma) is not a precipitin nor does it sensitize smooth muscle. Whether this is the same antibody that sensitizes skin and gives positive reactions after artificial sensitization in man (serum disease) or animal (anaphylaxis) has not been determined nor does any experimental approach presently appear available.

The moot question is whether the artificially produced antibodies in man and animal are one and the same, that is, is the precipitin the anaphylactic antibody? The majority of immunochemists working in

this field believe that it is and that the amount of precipitin is a measure of the sensitizing capacity of a serum. This is discussed by Kabat. It should be pointed out that present technics of active sensitization would be expected to stimulate all possible types of antibody concurrently and these would probably lie in the same protein fraction of serum and so might be separated with difficulty if at all. One tends to rely then on a quantitative correlation which does not always appear. The question of identity of precipitin, muscle-sensitizing and skin-sensitizing antibody cannot be fully resolved at this time.

The clinical value of the treatment of such allergies of the immediate wheal-type as hay fever has been established. By injections of the specifically reacting pollen extract, given over periods of several months, tolerance for the antigen is increased several hundred-fold and protection against clinical exposure is likewise increased.

Desensitization such as is produced readily in the anaphylactic animal does not obtain in the naturally sensitive man. In the early stages of treatment the amount of skin-sensitizing antibody in the serum is actually increased[45] and decreases only after prolonged treatment. A decrease of sensitivity of the tissues of the skin and conjunctiva is only partial at best and that only after weeks of treatment. The effect of therapeutic injections of specific allergens then may be spoken of rather as one of hyposensitization, possibly immunity, but not desensitization.

Blocking Antibody. Serologic studies[46] of patients treated for hay fever by means of specific pollen injections have shown the presence of a second antibody demonstrable by the fact that it has the capacity to inhibit the action of antigen on cellularly attached sensitizing antibody in skin sites when the serum of a treated patient is first mixed *in vitro* with the antigen and then used as the testing antigen. This is well shown in Table 1. Sites were made on the back of a normal test subject (D. L.) five each for ante- and post-treatment serum dilutions (1–10 to 1–500) for later testing with antigen. Sites were also made with the ante- or post-treatment serum to which antigen (ragweed extract) was added in the strength indicated (neutralization tests). The immediate reactions at these latter sites were read after one hour and it is

TABLE 1
COMPARISON OF ANTE- AND POST-TREATMENT SERUM (BUSCH)*
Normal Test Subject D.L. Used for Passive Transfer Test

Dilution Tests		Neutralization Tests			
Serum Dilutions† Ante-treatment	Reaction to test‡	Mixtures Made with Equal Amounts of§		Reaction of Sites	
1–10	+++	Busch Serum	Ragweed Units per ml.	1 Hr. after Sites Were Made	On Retest‖
1–100	++	Ante-treatment	50	+++	0
1–200	++	Ante-treatment	100	+++	0
1–300	+	Ante-treatment	150	+++	0
1–500	±	Ante-treatment	Saline	0	++++
Post-treatment	.....	Post-treatment	150	0	++
1–10	++	Post-treatment	300	0	++
1–100	++	Post-treatment	500	0	++
1–200	+	Post-treatment	700	0	++
1–300	0	Post-treatment	1000	±	+
1–500	0	Post-treatment	Saline	0	+++

* COOKE, R. A. *J. Allergy*, 15: 212, 1944.
† 1/10 ml. of the stipulated dilutions of serum in physiologic saline was injected into each site.
‡ The serum dilution sites were tested forty-eight hours later with 1/40 ml. low ragweed extract, 100 protein nitrogen units per ml.
§ 1/10 ml. of these serum-ragweed or serum-saline mixtures was injected into each site.
‖ The serum-ragweed or serum-saline mixture sites were tested forty-eight hours later with 1/40 ml. low ragweed extract, 100 protein nitrogen units per ml.

noted that there were reactions with ante-treatment serum antigen mixtures but none with mixtures made with post-treatment serum. When these same sites were retested two days later, even 50 units per ml. of ragweed extract neutralized the antibody in ante-treatment serum (since retests were all negative), but 1,000 units per ml. of ragweed failed to neutralize the post-treatment serum. This cannot be due to absence of antibody which was shown to be but slightly reduced by dilution test.

Such results are best interpreted as due to the development of an inhibiting or blocking antibody following treatment of

the patient with injections of pollen extract. There are several features that stamp this blocking antibody as distinct from the skin sensitizing antibody: (1) It may be produced easily in non-allergic persons by parenteral injection[47] whereas the skin-sensitizing antibodies have not been produced in this way. (2) It has further been shown that the blocking antibody, unlike the skin-sensitizing antibody, has no tissue affinity for it readily passes placental membranes[34] and is found in cord serum of infants from treated mothers. (3) It differs in that it binds antigen although it does not form a precipitate. (4) It has an almost absolute specificity which the skin-sensitizing antibody does not possess.[40] (5) The blocking antibody is thermostabile and unharmed at 56°c. for four hours[44] whereas the skin-sensitizing antibody is destroyed at this temperature.

Blocking Antibody and Immunity. It is still a moot question whether this blocking antibody produced by therapeutic injections is the important protective antibody or not. Except for the work of Loveless,[48,49] the studies[50,51] thus far have not indicated the degree of correlation between the amount of blocking antibody and the degree of clinical immunity that would seem to be required. My own unpublished observations are in accord with the latter studies. Admittedly these clinicoserologic studies are technically difficult and time-consuming and subject to the errors inherent in any appraisal based solely on the patient's impressions of his relative freedom from symptoms. Further, one must take into account the fact that there are at least several different and clinically active antigens in pollen extract with a blocking antibody specific for each.[40] None of the work thus far has taken this last fact into account. Also, patients who react to pollen extracts yet are clinically free, that is, immune in the real sense, frequently do not show blocking antibody in their serum.[40] They must therefore have some other as yet undiscovered protective mechanism. The fact that the blocking antibody has no cellular affinity makes it difficult to understand how it could protect the respiratory mucous membranes against airborne pollen whereas it could protect against injected (therapeutic) pollen extract, and this it may well do, thus permitting the increasing dosage during treatment. The studies of Sherman[45] strongly suggest this.

DELAYED ALLERGIC REACTIONS

There are three types of delayed reaction that may be differentiated for the present at least on certain obvious clinical and histologic grounds:

Tuberculin Type Allergy. Before the days of anaphylaxis and allergy, Koch[52] showed that tuberculous animals were reactive to the products of the growth of tubercle bacilli (tuberculin) which could produce either death or a local cutaneous reaction in the infected animal. This tuberculin skin reaction was a delayed twenty-four to forty-eight hour inflammatory response that was specific. Though bacterial protein may give rise to anaphylactic sensitization,[53,54,55] this delayed response was shown by Zinsser[56] to be entirely different. Animals cannot be made sensitive to tuberculin by injecting it in any amount, therefore tuberculin does not generate antibody production but merely reacts with preformed antibody. Though sensitivity to tuberculin could readily be created by injecting live tubercle bacilli, it was not until 1924 that Zinsser and Petroff[57] obtained positive results by intraperitoneal injections of massive doses of dead organisms. Eight to ten days are required for the incubation period for active sensitization. Having mastered the technic for the active production of tuberculin type allergy in non-tuberculous animals, which was facilitated by the use of such adjuvants as paraffin (Couland)[58] and paraffin oil (Saenz,[59] Freund[60]), the next question was whether this sensitivity could be passively transferred from sensitive to non-sensitive animals. Beginning with Baldwin's[61] work in 1910, all attempts were in vain until finally (1945) Chase[62] succeeded in the passive transfer of tuberculin sensitivity.

In his experiments normal guinea pigs were rendered sensitive to tuberculin by massive intraperitoneal doses of dead tubercle bacilli combined with the adjuvants above mentioned. Cells from spleen, lymph nodes and peritoneal exudate of the sensitive animals were washed thoroughly and injected into normal guinea pigs. In practically all experiments these animals became reactive to tuberculin in one to three days instead of the eight to ten days required for active sensitization, depending on the route of injection of the cells. The blood serum of the same actively sensitized guinea pigs did not transfer a sensitivity. Thus Chase has demonstrated conclusively that the mechanism for the tuberculin reaction involves a specific antibody that is strictly cellular, in other words, the reaction is an allergy (antigen-sensitized cell reaction). Rich[63] has shown that this cellular reaction is demonstrable in such avascular tissues as the cornea, hence is fundamentally different from the Arthus lesion which depends upon vascularity for its effects.

So far as is known, all bacteria are capable of producing the same specific sensitivity, hence the use of the modifying term "tuberculin-type." A similar skin test may be employed, therefore, as a diagnostic procedure in such other diseases as typhoid fever, brucellosis, tularemia, glanders, syphilis, certain fungus infections and in the viral infections causing lymphogranuloma venereum.

The diagnostic value of all such tests is lessened by the fact that sensitization persists after mild and cured infections, hence the test does not distinguish past from present and active infection.

Dermatitic-type Allergy. For many years certain forms of dermatitis such as infantile eczema have been hypothesized as allergies that is, antigen-sensitized cell reactions on the basis of clinical association with known allergies (asthma and food sensitivities) and because of the dermatitis produced in a few individuals upon slight external contact with chemicals, dyes, metals and plant phenols which are not irritating to the skin of most human beings. Such lesions when they occur are always delayed twenty-four to forty-eight hour reactions which may go on to vesiculation and exudation.

We are concerned here merely with the discussion of the immunologic aspects about which little is actually known as yet. The questions are, can antibody be demonstrated and if so, is it cellular or is it humoral, or may it be both? Landsteiner and Chase[64] produced dermatitis in guinea pigs which were sensitized by the application to the skin of picryl chloride. They used the peritoneal exudate to sensitize normal animals. When the picryl chloride in oil was put on the skin of these recipients, "erythematous reactions mostly of high color were apparent the next day." Heating, to kill the exudate cells, destroyed the effect. As they state, "consequently one would be inclined to assume that the sensitivity is produced by an activity in the recipient of the surviving cells, if not by antibodies carried by these."

A great deal of experimental work has been done, largely with external contact type dermatitis, in attempts to demonstrate the mechanism underlying these reactions. The experiments of Naegeli et al.[65] and Fellner[66] with excised portions of sensitive skin have given negative or equivocal results. However, Haxthausen[67] used transplants in two pairs of identical twins, one of each pair being sensitized with dinitrochlorobenzene. Skin flaps were transplanted from A (sensitized) to B (normal) and B to A, likewise from X (sensitized) to Y (normal) and Y to Z. When tested after three weeks, A and X gave strong reactions on the surrounding skin and on the graft whereas B and Y did not react either on the surrounding skin or on the previously sensitized skin flap. Such results certainly indicate a humoral antibody and may well explain the results reported from the use of blister fluid by Urbach,[68] Ballestero and Mom[69] and Spain.[70]

Recent work in my laboratory by Crepea, still unpublished, has shown the transference of dermatitic sensitivity from guinea

pigs sensitized by certain chemicals (plant phenols) to normal guinea pigs by means of the intraperitoneal injection of lymphoid and reticulo-endothelial cells of spleen and lymph glands and also by serum. The dermatitic lesion appears in normal animals within twenty-four hours after the injection of serums or washed cells whereas the incubation period for active sensitization is roughly two weeks and is elicited only by dermal application of the antigen.

Vascular-tybe Allergies. Rich[28,71] has reported lesions simulating Aschoff bodies and those of periarteritis in man after administration of heterologous serum and sulfadiazine in man and in rabbits after massive parenteral doses of foreign serum. Pathologically, there is also a resemblance to the Arthus lesions of rabbits. The immunologic mechanism of these reactions is confused just as it was in the past in the case of the tuberculin and the anaphylactic types of reaction with tuberculo-protein. The technic of creating vascular lesions at present produces the anaphylactic antibodies concomitantly. The fact is that the vascular degenerations are delayed reactions as opposed to the immediate anaphylactic reactions. Whether there is a different antibody mechanism for the two remains to be determined.

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Quantitative Immunochemical Aspects of Some Allergic Reactions*

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WHILE the concept of allergic reactions as caused by the combination of antigen with antibody in the tissues is unequivocally established (for earlier studies,[1-5]) knowledge of the severity of the allergic response as a function of the amounts of antigen and antibody involved is quite limited. Indeed there have been sharp differences of opinion among various investigators as to the dependence of the Arthus phenomenon on circulating antibody,[6] the relative significance of humoral and fixed tissue antibody in the various allergic manifestations,[7] whether or not circulating antibody protects guinea pigs against anaphylactic shock,[8] the nature of the refractory state following non-fatal anaphylactic shock[8] and the role of precipitins in serum sickness.[9]

Careful scrutiny of the mass of experimental data reported suggests a number of reasons for these discordant opinions. Among these are: (1) The use of complex mixtures of antigens, such as horse serum, with the resultant simultaneous production in varying quantities of antibody to an unspecified number of antigens; (2) the tremendous variation in antibody response of individual animals of the same species to a given quantity of antigen, so that very large numbers of animals must be used for statistically valid differences to be detected; (3) species differences in allergic manifestations, in the amounts of circulating antibody formed, and in the capacity of sera of various species to transfer certain sensitivities passively to some species but not to others;[1] (4) limitations of immunologic methods of assaying sera for antibody and (5) non-specific factors such as the inhibition of anaphyaxis by the injection of foreign protein. This effect led Weil[10] erroneously to the conclusion that an excess of antibody in the circulation protects a guinea pig from anaphylactic shock. Weil injected rabbit serum containing antibodies into guinea pigs sensitized to the corresponding antigen and found that they were protected against anaphylactic shock. As pointed out by Bronfenbrenner,[8] equally good protection would have resulted had an equivalent amount of normal rabbit serum or of normal serum from another species been used.

The need to take these variables into account has not escaped the attention of certain investigators. Cannon and Marshall,[6] in their study of the Arthus phenomenon, point out that a correlation between the severity of the Arthus phenomenon and the circulating precipitin was found with purified single antigens, i.e., crystalline egg albumin, while discordant results were obtained with mixtures of antigens (whole serum). The unsuitability of the antigen dilution method of estimating the precipitin content of sera for such studies has also been noted,[6] as has the superiority of passive anaphylaxis over active anaphylaxis as a means of eliminating the variations in the quantities of antibody produced by individual animals in response to injection of antigen.[8]

Since methods for the quantitative estimation of antibodies in terms of the amount of antibody nitrogen per ml. serum are now

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readily available,[11-13] measurements of the amount of antibody in the circulating blood of an animal immediately prior to or after eliciting an allergic response are easily carried out. In studies on passive sensitization, sera may be assayed for their antibody content and dilutions containing known amounts of antibody may be injected. Similarly, the allergic response may be elicited by injection of a known quantity of antigen. These procedures, if generally adopted, would provide a degree of standardization and reproducibility in results from different laboratories which would do much to avoid conflict and confusion.

TABLE 1

RELATION BETWEEN CIRCULATING ANTI-EGG ALBUMIN AND THE SEVERITY OF ANAPHYLACTIC SHOCK INDUCED IN THE ACTIVELY SENSITIZED RABBIT WITH CRYSTALLINE EGG ALBUMIN *

Degree of Anaphylaxis	No. of Animals	Antibody Nitrogen Content of Individual Rabbit Sera before Shock
		mg./ml.
Death	8	0.57[3], 0.9, 1.0, 1.2, 2.1, 2.3
+++	5	0.11, 0.46[2], 1.0, 2.1
++	6	0.06, 0.28, 0.34, 0.57, 1.1
+	11	0.03[2], 0.06[2], 0.11, 0.16, 0.28, 0.57, 0.80, 1.0, 1.1
0	20	0.02[2], 0.03[2], 0.04[2], 0.11[2], 0.28[4],0.34[3], 0.46, 0.57[2], 0.90, 1.5

+++ = Severe prostration and shock.
++ = Respiratory difficulties, slight prostration.
+ = slight respiratory difficulties.
0 = No reaction.

Superscripts denote number of rabbits having the same antibody N level. Shocking doses of egg albumin N varied from 2.5 to 40.5 mg. and did not appear to be critical.

* Data from Jackson.[14] Values converted to antibody nitrogen, i.e., 16 per cent of antibody protein and expressed to two significant figures.

The earliest attempt to estimate the quantities of antibody in the circulating blood of sensitized animals was made by Jackson[14] who studied the severity of anaphylactic shock in rabbits actively sensitized to crystalline egg albumin in relation to the amounts of antibody in their sera. From her data (Table 1) it is evident that in the actively sensitized rabbit there is only the most general correlation between the amount of circulating antibody and the severity of anaphylactic shock in the rabbit and that a high level of circulating antibody does not necessarily ensure fatal anaphylaxis. Indeed, of the ten rabbits having levels of 1.0 mg. antibody N per ml. serum or more, only four showed fatal reactions; one negative and two one plus reactions were obtained. Jackson further found that the amount of antigen necessary for fatal anaphylaxis was not decisive. In four of the eight rabbits dying of anaphylaxis, insufficient antigen to remove all of the circulating antibody was used while nineteen of twenty-one rabbits which failed to die in anaphylaxis received injections of egg albumin sufficient to remove all of the circulating antibody. In the rabbit, factors other than the quantities of antibody appear to be of importance in determining the outcome of anaphylactic shock.[15]

At about the same time Culbertson[16] studied the severity of the Arthus phenomenon in rabbits actively immunized with crystalline egg albumin as a function of the amounts of anti-egg albumin in the circulation. As the level of circulating antibody rose following the last injection of antigen, the Arthus reaction tested on successive days became of increasing severity. With levels of circulating antibody of 0.08 mg. N per ml. or less, only mild reactions occurred, characterized by transient erythema and superficial scaling, while with levels of 0.12 to 0.16 mg. antibody N per ml. a slough was invariably obtained. When animals were allowed to rest until antibody was no longer demonstrable in their circulation, the Arthus reaction became negative. Similarly, negative reactions could be obtained temporarily by complete removal of antibody from the circulation by intravenous injection of sufficient antigen; upon reappearance of antibody positive Arthus tests again occurred.[16]

Culbertson[16] was also the first to elicit the Arthus phenomenon passively with known amounts of antibody nitrogen. Injection of 0.047 mg. of egg albumin N intracutaneously into a rabbit one-half

hour after the animals had received an intravenous injection of 15 mg. of anti-egg albumin N resulted in a strongly positive Arthus reaction with a marked slough. Arthus reactions characterized by erythema and edema but with no slough resulted from intracutaneous injection of 0.75 and 0.075 mg. anti-egg albumin N followed one-half hour later by 0.047 mg. of egg albumin N. A reversed Arthus reaction consisting of erythema, edema and necrosis resulted from intravenous injection of about 10 mg. of egg albumin N followed by intracutaneous injection of 0.38 mg. of anti-egg albumin N. In all instances absorption of the antibody from the serum with antigen prior to injection abolished its capacity to produce an Arthus reaction.[16]

While these two earlier studies clearly demonstrate the superiority of studying allergic reactions in terms of the actual quantities of antibody and antigen involved, they did not provide sufficient data to establish the minimum quantities of antigen and antibody required for these reactions.

Further studies along these lines have been carried out in the writer's laboratory. In a study on passive anaphylaxis with Landow,[17] the minimum quantities of rabbit anti-egg albumin (Ea) N or rabbit anti-SIII N (antibody to the specific polysaccharide of the type III pneumococcus) were determined which were required to sensitize a 250 Gm. guinea pig so that uniformly fatal anaphylactic shock would result on subsequent injection of a given amount of Ea N or of SIII forty-eight hours later. Both sensitizing and shocking doses were given intravenously. The antisera were analyzed for antibody N by the quantitative precipitin method and dilutions of antiserum containing the desired quantities of antibody were injected. From Table II it is seen that sensitization with about 0.03 mg. of anti-Ea N or anti-SIII N is sufficient to produce uniformly fatal anaphylactic shock when followed by a subsequent intravenous injection of 0.16 mg. EaN or 0.10 mg. SIII, respectively. With sensitizing levels of 0.006 to 0.025 mg. antibody N anaphylactic symptoms are usually observed but fatal reactions do not always occur. With even smaller quantities of antibody, none of the animals die and some may even fail to show symptoms of anaphylaxis.

Since these data represented passive sensitization of guinea pigs with serum of another species, a similar study was carried out with anti-Ea produced in the guinea pig.[18] Since the guinea pig does not readily give rise to sufficient amounts of precipitin by the usual method of immunization, the Freund adjuvant technic[19] was employed. As shown in Table III, guinea-pig anti-EaN was equally effective as rabbit anti-EaN in passive sensitization. This finding makes it probable that, in sensitization

TABLE II
PASSIVE SENSITIZATION OF GUINEA PIGS WITH VARYING AMOUNTS OF RABBIT ANTIBODY*

Antibody N Injected	No. of Guinea Pigs Used	Results			
		Deaths	Severe Reactions	Slight Reactions	No Reactions
Rabbit anti-egg albumin—guinea pigs shocked with 1 mg. egg-albumin intravenously 48 hours after sensitizing injection					
mg.					
0.0019	4	0	0	2	2
0.0038	4	0	1	3	
0.0057	5	0	3	2	
0.0064	1	1			
0.0075	4	0	3	1	
0.0113	6	4	2		
0.023; 0.024	5	3	2		
0.034; 0.036	6	6			
0.048	2	2			
0.06	8	8			
0.072	1	1			
Rabbit antibody to type III pneumococcus—guinea pigs shocked with 0.1 mg. type III polysaccharide intravenously 48 hours after sensitizing injection					
0.01	4	1	2	1	
0.02	5	4	1		
0.03	4	4			
0.04	4	4			

* From Kabat and Landow.[17]

with heterologous sera, the non-antibody protein injected together with the antibody does not affect its sensitizing capacity although it has been well established that a previous injection of serum of a foreign species inhibits anaphylactic shock.[8]

TABLE III
PASSIVE SENSITIZATION OF GUINEA PIGS WITH VARYING AMOUNTS OF GUINEA PIG ANTI-OVALBUMIN—GUINEA PIGS SHOCKED WITH 1 MG. OVALBUMIN INTRAVENOUSLY 48 HOURS AFTER SENSITIZING INJECTION*

Antibody N Injected Mg.	No. of Guinea Pigs Used	Results				
		Dead	Severe	Moderate	Slight	Negative
0.005	6	..	2	2	2	
0.006	4	..	3	1		
0.010	7	5	2			
0.012	4	1	2	1		
0.015	7	6	1			
0.018	4	4				
0.020	8	7	1			
0.024	5	3	2			
0.030	8	8				
0.036	4	4				
0.040	10	10				
0.048	3	3				

* From Kabat and Boldt.[18]

In a more extensive study of passive anaphylaxis,[20] the severity of anaphylactic shock produced by varying quantities of antigen was studied at several sensitizing levels of antibody nitrogen. In the egg albumin rabbit anti-egg albumin system, it was found (Table IV) that an increase in the sensitizing dose from 0.03 to 0.15 mg. antibody N did not significantly change the quantity of antigen required to kill one-half of the animals; a further increase to 0.75 mg. antibody N, however, resulted in a five-fold increase in the antigen needed to produce 50 per cent anaphylactic deaths. In the SIII-anti-SIII system, however, similar variation in the sensitizing dose did not appear significantly to affect the quantity of antigen required for 50 per cent mortality. (Table IV.)

With tobacco mosaic virus and its homologous rabbit antibody, fatal anaphylaxis could be obtained in guinea pigs sensitized with 0.03 mg. of antibody N only when the shocking dose was increased to 3.6 mg. N, many times more than was needed in the Ea-anti-Ea system. This is most reasonably ascribed to the higher molecular weight of tobacco mosaic virus (33,000,000) as compared with egg albumin (40,000) from which it follows that an equal weight of virus would contain many fewer molecules than would egg albumin. It is also in accord with the finding that the ratio of antibody N/antigen N at the point of maximum precipitation is about twenty times greater in the ovalbumin system than in the tobacco mosaic virus system.

Follensby and Hooker[21] reported that four of six guinea pigs sensitized with 0.12 to 0.48 mg. rabbit anti-hemocyanin suffered fatal anaphylactic shock on injection of ten to forty-seven times the quantity of antigen optimal *in vitro* for complete precipitation of the antibody in the sensitizing dose; of the remaining animals one showed severe and the other mild anaphylaxis.

The quantitative relations in passive anaphylaxis have also been studied for a cross-reaction—the reaction between S VIII and rabbit anti-SIII.[20] In this system the amount of cross-reacting antibody N was determined and dilutions of antiserum containing known quantities of cross-reacting antibody N were injected. It is evident from Table IV that on sensitization with 0.03 mg. of cross-reacting antibody N, fatal anaphylactic shock could not be obtained, as it was in the homologous reaction, even when the antigen was varied from 0.005 to 4.0 mg. With larger sensitizing doses of antibody N, reactions of increasing severity were obtained with a shocking dose of 0.10 mg. of S VIII and uniformly fatal anaphylactic shock was found with 0.20 and 0.35 mg. cross-reacting antibody N. These results are in accord with quantitative precipitin studies on this system[22,23] in which the cross-reaction was found to involve fewer reactive groups on the antibody molecule than did the homologous reaction.

TABLE IV

QUANTITATIVE RELATIONSHIPS BETWEEN AMOUNTS OF ANTIBODY AND ANTIGEN USED AND THE SEVERITY OF PASSIVE ANAPHYLAXIS IN THE GUINEA PIG*

Antibody N Injected for Sensitization, Mg.	Antigen Injected to Elicit Shock									Approximate Amount of Antigen to Produce 50 Per Cent Mortality,† Mg. N
	0.16 Mg. N	0.12 Mg. N	0.08 Mg. N	0.04 Mg. N	0.02 Mg. N	0.01 Mg. N	0.0075 Mg. N	0.005 Mg. N	0.001 Mg. N	
					Ovalbumin Rabbit Antiovalbumin					
0.030	.....	6 dead	3 dead 2 severe	4 dead‡ 1 severe	3 dead	9 dead	3 dead 1 severe 1 moderate 1 slight	4 dead 2 severe 1 moderate	.....	0.007
0.15	4 dead	.....	3 dead	6 dead	7 dead	6 dead 1 severe 1 moderate	2 dead 6 severe 2 moderate 1 slight	1 dead 2 moderate 3 slight	..... 2 slight 1 negative	0.008
0.75	3 dead	2 dead	6 dead	2 dead 1 severe 1 moderate	1 dead 1 severe 2 moderate	..... 2 slight 1 negative	..... 1 slight	.....	.....	0.04

Antibody N Injected for Sensitization, Mg.	3.6 Mg. N	1.2 Mg. N	0.42 Mg. N	0.22–0.24 Mg. N	0.16–0.18 Mg. N
		Tobacco Mosaic Virus Rabbit Anti-tobacco Mosaic Virus			
0.030	2 dead	1 severe	.....	1 moderate	2 moderate
0.10	1 dead	1 moderate 1 slight	....	1 severe 2 slight§	1 slight
0.20	.....	1 slight 1 doubtful	1 severe 1 doubtful		

Antibody N Injected for Sensitization Mg.	0.10 Mg.	0.075 Mg.	0.05 Mg.	0.025 Mg.	0.01 Mg.	0.0075 Mg.	0.005 Mg.	0.0025 Mg.	0.001 Mg.	Approximate Amount of Antigen to Produce 50 Per Cent Mortality,† Mg. N
					SIII Rabbit Anti-SIII					
0.030	7 dead‖	7 dead	7 dead 1 severe	6 dead 1 severe	1 dead 2 severe 1 moderate	4 dead 2 severe	2 dead 1 severe 1 moderate	1 moderate 1 slight 2 negative	.....	0.008
0.15	.....	.....	4 dead	.....	5 dead	16 dead	6 dead 5 severe 1 moderate 2 slight	1 severe 1 moderate 1 slight 2 negative	1 moderate 1 slight 5 negative	0.005
0.75	2 dead	.....	.....	7 dead	2 severe 2 slight 1 negative	2 dead 1 severe	1 dead 2 moderate	....	2 slight 2 negative	0.01±

Cross Reacting Antibody N Injected for Sensitization	4.0 Mg.	3.5 Mg.	2.0 Mg.	1.0 Mg.	0.50 Mg.	0.40 Mg.	0.20 Mg.	0.10 Mg.	0.005 Mg.
					SVIII Rabbit Anti-SIII				
0.030	1 moderate	1 moderate	2 slight	1 moderate 1 slight	1 severe 1 moderate 1 slight	....	....	2 doubtful 2 negative	2 slight 1 doubtful 2 negative
0.050	.....	.....	.....	.....	.....	1 dead 1 moderate	2 severe 1 moderate	4 severe	
0.060	.....	.....	.....	2 dead 2 severe	.....	.....	.....	1 dead 1 severe 1 moderate 1 slight	
0.10	.....	.....	.....	.....	.....	6 dead	.....	3 dead 3 severe 1 slight	
0.20	.....	.....	.....	.....	.....	.....	.....	5 dead	
0.35	.....	.....	.....	.....	.....	.....	.....	4 dead	

* From Kabat, Coffin and Smith.[80]
† Estimated by inspection; essentially similar results derived from statistical considerations.
‡ 1 delayed death.
§ 1 animal received 0.30 mg. antigen N.
‖ Including data from (17).

Passive anaphylaxis studies with measured quantities of antibody nitrogen are especially useful in clearly establishing differences in the capacity of sera of various species to confer passive sensitivity. For instance, it is readily evident from the studies of Follensby and Hooker[21] under what conditions passive sensitization of guinea pigs with equine anti-hemocyanin and equine anti-egg albumin could not be obtained; and it is conceivable that the finding of Bailey and co-workers[24,25] that guinea pigs could be passively sensitized with horse anti-pneumococcal antibody, which appear to be contradicted by the studies of all other workers,[26–28] might be explained by differences in the quantities of antibody N used by the various workers for sensitization. If known quantities of antibody N were used in standardization of passive anaphylaxis for estimating small amounts of polysaccharides as proposed by Morgan,[29] this would also serve to ensure reproducibility between different laboratories and with different lots of sera. These standardized conditions for passive anaphylaxis have also proved of value in studying the effects of various unrelated substances on anaphylaxis. For instance, Coffin and Kabat[30] used this procedure in demonstrating that immunization with histamine azoprotein or with normal human serum protects guinea pigs against fatal anaphylactic shock indicating that the protection was not specific for histamine azoprotein.

Quantitative studies have also provided an estimate of the weights of antibody which must be present in isolated muscle tissue for anaphylactic contractions to occur. Studies on isolated uterine horns of a limited number of female guinea pigs sensitized by injection of known quantities of anti-EaN showed that, on addition of 0.16 mg. EaN to the bath, good contractions were obtained in two animals sensitized with 0.03 mg. antibody N, in one of two sensitized with 0.02 mg. antibody N and in one of three sensitized with 0.01 mg. antibody N. These findings suggest that the sensitivity of the isolated guinea pig uterus is of the same order as that of the intact animal.[19] If the intravenously injected anti-EaN is uniformly distributed throughout the tissues of the guinea pig, as appears reasonable from Freund's studies,[31–34] a contracting guinea pig uterine horn (wt. 75 mg.) would contain only 0.01 μg. antibody N of the 30 μg. antibody N injected into the 250 Gm. guinea pig. This quantity of antibody N is considerably less than can be detected by *in vitro* serologic tests and may perhaps provide an explanation for the failure of the sera of hypersensitive patients to give the usual serologic tests for antibody.

Additional information on the conditions under which anaphylactic shock occurs in the guinea pig may be obtained by bleeding guinea pigs injected with known quantities of antibody N at the time when the shocking dose of antigen would ordinarily be given and determining the amount of circulating antibody by the micro-quantitative precipitin method[11–13,35] after removal of complement.[36] Data of this kind have been obtained for the Ea-anti Ea and SIII-anti SIII systems.[20] Table v shows the quantities of antibody N in the circulation forty-eight hours after 30, 150, and 750 μg. anti-EaN or anti-SIII N were injected into guinea pigs. With anti-Ea, it is evident that significant quantities of circulating antibody did not remain in the circulation when 30 or 150 μg. anti-EaN was injected but that a considerable proportion of the total antibody was present in the blood forty-eight hours after 750 μg. anti-EaN were given. By comparison with the data in Table iv, it would appear that the increased quantity of antigen required to kill one-half of the guinea pigs sensitized with 750 μg. anti-EaN might be attributed to a protective effect of circulating antibody. In the SIII-anti SIII system, however, about 30 to 50 per cent of the injected antibody remained in the circulation at the time of shock and no evidence of a significant increase in the shocking dose of SIII was found. (Table iv.) The reasons for the apparent protective action of circulating antibody in the

Ea-anti Ea system and the absence of such an effect in the SIII-anti SIII system require further investigation.

Quantitative data have also been obtained relating the severity of the Arthus reaction, induced passively in the rabbit, anti-EaN and the severity of the reaction increased with the quantity of antibody. (Table VI.) With animals sensitized intracutaneously with antibody, the reaction was of comparable degree even if antigen was given intravenously and no significant

TABLE V

RELATION BETWEEN ANTIBODY NITROGEN INJECTED INTRAVENOUSLY INTO GUINEA PIGS AND THE QUANTITY IN THE SERUM 48 HOURS LATER*

Guinea Pig	Serum Volume,† Ml.	Antibody N Injected Intravenously, μg.	Antibody N in Serum 48 Hours Later, μg./ml.	Total Circulating Antibody N 48 Hours Later, μg.	Guinea Pig	Serum Volume,† Ml.	Antibody N Injected Intravenously, μg.	Antibody N in Serum 48 Hours Later, μg./ml	Total Circulating Antibody N 48 Hours Later, μg.
Rabbit anti-egg albumin					Rabbit antibody to pneumococcal polysaccharide, type III				
1	11	30	0.0	0	21	10.5	30	1.0‡	10.5‡
2	11	30	0.0	0	22	9	30	1.2‡	11‡
3	8	30	0.0	0	23	10	30	0	0
4	8	30	0.0	0	27	9.5	30	2.3§	22
5	8	30	0.6‡	5‡	28	10	30	0.6‡	6‡
6	10	150	0.4‡	4‡	17	10	150	7.5	75
7	12	150	0.9‡	11‡	18	11	150	4.0	44
9	11	150	1.3‡	14‡	19	11.5	150	6.4	74
15	13	150	0.8‡	10‡	20	12	150	4.2	50
10	8.5	750	17.6	150	24	9	750	28.5	255
11	10.5	750	2.5	25	25	9.5	750	32.0	305
12	11	750	29.0	320	26	9.5	750	24.2	230
13	9	750	33.0	300					
14	8	750	3.9	30					
29	10.5	750	14.9	155					
30	11	750	5.1	55					

* From Kabat, Coffin and Smith.[20]
† 1/25 of body weight taken to the nearest 0.5 ml.
‡ Values of less than 1–2 μg. N/ml. are within experimental error.
§ One determination lost.

to the quantities of EaN and anti-EaN.[37] After preliminary experiments, the interval of one-half hour between the sensitizing and shocking doses, as employed by Culbertson,[16] was adopted as most satisfactory. When the antibody and antigen were administered intracutaneously, it was found that the severity of the reaction was determined primarily by the quantity of antibody and was rather insensitive to the amount of antigen once a threshold quantity was exceeded. Minimal Arthus reactions were obtained by local injection of 0.025 mg. differences in the intensity of the responses were observed with reversed as compared with direct local Arthus reactions. (Table VI.)

When the antibody was administered intravenously and the antigen locally, considerably larger amounts of antibody were required for a minimal Arthus response. In only one of two rabbits which received 1.12 mg. anti-EaN intravenously could a minimal Arthus reaction be elicited. With two and four times this quantity of antibody N, reactions increasing in intensity

resulted. Culbertson[16] was able to produce a slough by intravenous injection of 15 mg. anti-EaN.

The passive Arthus phenomenon in the rabbit, therefore, appears to differ sharply from passive anaphylaxis in the guinea pig. as much, to contract on addition of antigen. Even if these values are corrected for the different weights of tissue participating, induction of the Arthus reaction clearly requires many times more antibody than does local anaphylactic shock.

TABLE VI

RELATIONSHIP BETWEEN SENSITIZING AND SHOCK DOSES ON SEVERITY OF THE PASSIVELY INDUCED ARTHUS REACTION IN LOCALLY SENSITIZED RABBITS*

Anti-egg Albumin Nitrogen Mg.	Egg Albumin Nitrogen, Mg.										
	0.5	0.25	0.13	0.06	0.03	0.015	0.008	0.004	0.001	0.0005	0.0001
0.9	++++	++++	++++ ++++ ++++ ++++	+++							
0.67	.....	.....	++++ ++++ ++++								
0.45	.....	++++ [+++]	++++ ++++ ++++	+++ [++++]	....	+++ [++++]	....	+++	± +++ [+++]	± + [++] [++]	0
0.22	++++	++++ ++++ +++	++++ ++++ ++++ +++ [++]	++++ ..... +++ ++ [+++]	....	+++ .... [++]	....	+++	++ ..... ++ ..... [++]	+ ++ ..... [+] [++]	0 [+]
0.15	.....	+++ ++	+++ ++	+++ +++	+++ +++	+++ +++	+++ +++				
0.10	.....	+++ ++	+++ ++	+++ ++	+++ ++	+++ ++	+++ ++				
0.05	.....	++ ++ [+++]	+	++ + [+]	++	+ + [++]	++	+	±		
0.025	.....	+ + [+]	+ + ...	+ + [+]	+ + ...	+ + [+]	+ + ...	+ + + ±	++ [+]	± [+]	0 [0]
0.01	.....	0 0 [0]	0 0	0 0 [±]	0 0	0 0 [0]	0 0	.....	+ [+]	± [+]	0 [0]

*From Fischel and Kabat.[27]

In the former instance, 25 μg. of antibody N was required for a minimal local reaction while it was calculated that a strip of guinea pig uterine muscle need contain about 0.01 μg. antibody N, or only $\frac{1}{2500}$

Thus far, anaphylaxis and the Arthus phenomenon are the only allergic reactions for which quantitative data are available. It should not be too difficult to extend these studies to at least several other allergic

manifestations and to compare the amounts of antigen and antibody required to elicit these reactions in different species. The finding of Mehlman and Seegal[27] that horse antibody to the pneumococcal polysaccharides, while not conferring anaphylactic sensitivity, would sensitize so that a wheal and erythema type of response would be induced in the guinea pig on subsequent injection of polysaccharide deserves such quantitative treatment; and the subsequent report by Mehlman[38] that passive anaphylaxis could be induced in dogs sensitized with horse or rabbit anti-pneumococcal serum also merits quantitative study. Indeed, quantitative studies on the sensitizing properties of the antibodies produced in guinea pigs and rabbits with low molecular weight simple substances, such as citraconic anhydride[39] and others,[39,40] might further broaden our concepts to include the drug allergies.

The most severe limitation to the extension of this approach to the study of the quantitative aspects of human allergic reactions is the complex nature of the antigenic mixtures used in testing for hypersensitivity and failure thus far to find any *in vitro* reactions of antibodies which are amenable to quantitative immunochemical study in the sera of individuals with the common allergies. It is possible that as more sensitive immunochemical methods of measuring antibody are developed *in vitro* tests may be obtained. Perhaps the study of the sera of individuals sensitive to horse serum will prove of value in this connection; in one such serum quantitative measurements of precipitin have recently been made.[41] In any event, a comprehensive picture of the quantitative aspects of the various allergic reactions in different animal species should serve as a convenient framework within which much of our knowledge can be coordinated.

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Rôle of Histamine in Anaphylaxis and Allergy*

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IT was recognized early in the study of anaphylaxis that the symptoms produced by the injection of a foreign protein into a previously sensitized animal could best be explained on the basis of an explosive release of some toxic substance. Following the isolation of histamine from ergot,[1] Dale and Laidlaw[2] came to the conclusion that its pharmacologic effects in animals closely resembled those observed in anaphylactic shock and ventured the opinion that histamine might indeed be released in the latter phenomenon. When histamine was shown to be a normal constituent of tissues,[3] this possibility seemed even more likely and, in 1927, Dale[4] proposed the theory that histamine is liberated from the tissues of animals by cell stimulation resulting from the interaction of antigen with antibody. He was careful to point out that histamine existed in cells as such and was released not formed by this mechanism. In 1908, Von Pirquet[5] emphasized the close relationship between anaphylaxis and allergy and, in 1927, Sir Thomas Lewis[6] published his now classical observations on the triple response and H- or histamine-like substance.

So great was the impetus to clarify this whole subject that a relatively enormous literature has grown and many reviews on the subject have appeared, the most recent being those by Feldberg,[7] Dragstedt,[8] Code,[9] Rocha e Silva,[10] Selle,[11] Rose,[12] and Feinberg.[13] The present review is an attempt to consider some of the recent work on this subject as well as certain aspects of histamine metabolism which may be pertinent to the discussion as a whole. In this connection, two facts should be borne in mind: The first is that relatively little is known of the physiologic significance of histamine and the second is that most of our knowledge of its activity in allergic states is of an indirect nature. Practically all of the investigations which have been made rely on a biologic method of assay; and while it is generally agreed that histamine as such is being estimated, final proof must await chemical identification.

METABOLISM

Histamine is derived from histidine, one of the essential amino acids, by decarboxylation. In support of this, Anrep et al.[14] were able to demonstrate an increase in the histamine excretion in the urine of patients to whom food was fed that was high in histidine. Normally, however, it is probable that this breakdown occurs in the intestine by the action of suitable bacteria. Histamine may be excreted, apparently unchanged, in the urine or inactivated by histaminase, an enzyme first isolated by Best[18] from lung tissue. It may also be inactivated by tissues which do not contain histaminase such as the kidney and liver of the rat.[19] The metabolism of histamine is under the influence of certain endocrine glands. Rose and Browne[20] noted an increase in the histamine content of the tissues of the rat following removal of the adrenal glands and this was confirmed by Marshall.[21] The histamine content of the blood is also increased in both the rat[21] and rabbit[22] under these conditions. According to Gotzl and Dragstedt,[23] thyroidectomy results in a decrease of the histamine content of the skin

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and tissues of the rat whereas the administration of thyroid extracts increases its content in these tissues. It is of interest to note that removal of these glands results in a decreased resistance to histamine[24,25] as well as to anaphylactic shock.[26–28]

DISTRIBUTION IN TISSUES

Histamine has been isolated in the crystalline state from animal tissues by Best, Dale, Dudley and Thorpe[3] and, more recently, by Code and Ing[29] from the blood of the rabbit. Using various biologic methods of assay, it has been shown to be present in most animal tissues but predominantly in the so-called "shock" tissues such as the lungs of the guinea pig and the liver of the dog. In the mouse over 60 per cent is found in the skin.[30] The blood of most animals contains histamine, the highest amount being found in the rabbit and the lowest in the cat.[31] In man, using Code's modification[32] of Barsoum and Gaddum's method,[33] most workers have found the blood histamine content to vary from 2 to 7γ/100 cc. expressed as base.[34–36] It is also present in small amounts in cerebrospinal fluid.[37] In a study of the histamine content of gastric mucosa in man Trach, Code and Wangensteen[38] found an average of 10.2 mg. per Kg. in the antral portion and 5.8 mg./Kg. in the fundus. Pellerat[17] has recently shown that the histamine content of the skin of normal man varies from 16 to 24 mg./Kg. Although the tissue of the central nervous system is virtually devoid of histamine, Kwiatkowski[39] found it to be present in large amounts in the peripheral sensory nerves. It is of interest that these are the only nerves capable of antidromic stimulation.

Of great importance, however, is the disposition of this histamine. Like other metabolites, such as potassium, the major portion of blood or tissue histamine is either bound to or held within the cell. It was first demonstrated by Code,[40] and later confirmed by others,[40–42] that 70 to 90 per cent of the blood histamine is held in an inactive state within the white blood cell elements, the small remainder circulating in a free state in the plasma or held within the red blood corpuscles. Tissue histamine, such as that of the lungs or liver, is held in a similar manner within the tissue cells.[43,44] It will be obvious, therefore, that in this bound and inactive form histamine constitutes a ready source of a powerful toxic substance capable of instant action on release.

PHYSIOLOGY AND PHARMACOLOGY

It is not known what rôle histamine may play in the economy of the organism. From the evidence at hand it seems likely that along with other vasodilator substances it forms part of the control mechanism of the circulation, balancing the action of vasoconstrictor substances such as adrenalin. In support of this concept, Feldberg[45] as well as others[46] have shown that the injection of histamine will stimulate the release of adrenalin from the medulla of the adrenal gland. Furthermore, Staub[47] has demonstrated that the intravenous injection of adrenalin in man will produce an increase of the histamine content of the blood plasma. Since plasma histamine is active, Staub[48] suggests that this reciprocal relationship is part of the regulatory mechanism of the circulation. It is believed by some that the secretion of hydrochloric acid by the gastric mucosa may be mediated by histamine.[49] While there is no conclusive evidence to support this theory, McGavack et al.[50] were able to suppress completely hydrochloric acid secretion in man by three to four weeks administration of benadryl, an antihistamine substance, in high dosage.

Pharmacologic studies on the actions of histamine are countless, for there is hardly an organ or tissue which will not respond in some way to this substance. For the present purpose, however, it will suffice to remember its four main properties. These are, that it produces contraction of smooth muscle, that it produces dilatation of capillaries and venules in most species and, in man, the arterioles as well, that it markedly increases capillary permeability and that it is a potent stimulator of glandular secretion. It will become apparent immediately that

these properties could account for many of the symptoms and signs of anaphylaxis as well as those of allergy. In the latter, the constriction of the bronchioles and secretion of mucus is prominent in asthma. Dilatation and increased permeability of the capillaries are the basic changes in urticaria as well as those seen in vasomotor rhinitis. Similarly, in anaphylactic shock in most animal species the major changes observed may be reproduced by the administration of histamine and, as previously pointed out, it was this similarity in action of the two conditions, namely, histamine intoxication and anaphylactic shock, which led Dale to formulate the theory of histamine as the mediator of anaphylaxis and allergic symptoms. Yet, as will be discussed later, there is increasing evidence that other factors must play a rôle as well.

METHODS OF DETERMINATION

The original method of Barsoum and Gaddum,[33] as modified by Code,[32] has been used by the majority of recent investigators for the determination of histamine in blood and tissue. It is assumed that histamine as such, whether in the free or bound form, is being extracted. Some doubt has been cast on this assumption by the recent work of Rocha e Silva,[51] who has made use of chemical combinations of histamine bound to amino acids by peptide linkage. Pharmacologically, such compounds are inactive. Yet when they are subjected to the Code method of extraction, the histamine component is recovered quantitatively in an active form.[10] It is possible, therefore, that the whole blood and tissue values, as determined by Code's method, are made up of inactive histamine bound to other amino acids as well as of free histamine itself. Furthermore, Pellerat[17] claims to have shown that a smooth muscle contracting substance may be extracted from urine by the Code method in addition to histamine. This substance, which ordinarily would be regarded as histamine, can be distinguished by the fact that its activity is not inhibited by antihistamine compounds nor is it inactivated by histaminase. How far these observations can be extended to results reported by others will have to await further confirmation. In this review, however, these histamine-like substances are referred to as histamine base, in gamma per 100 cc. of blood or other fluid or gamma per Kg. of tissue.

ANAPHYLAXIS

There can be no doubt that histamine plays a major rôle in the phenomenon of anaphylaxis in most animal species. However, it must be emphasized at the outset that the histamine theory does not pretend and never claimed to reduce all the manifestations of the antigen-antibody reaction to histamine effects.[53] The first demonstrations of histamine release as a result of antibody-antigen reaction were made independently in 1932. Bartosch, Feldberg and Nagel[54] showed the release of histamine from the isolated, perfused lungs of the sensitized guinea pig following addition of the specific antigen to the perfusing solution. Dragstedt and Gebauer-Fuellnegg[55] were successful in demonstrating large amounts of histamine in the blood and lymph of the dog rendered anaphylactic. It was not, however, until 1939 that Code[56] recorded the quantitative release of histamine into the blood of these two species thus firmly establishing histamine as a major factor in the production of symptoms and clarifying the sequence of events.

A consideration of anaphylaxis in relation to the histamine theory still leaves certain discrepancies unanswered. The guinea pig, perhaps of all animal species investigated, has until recently fulfilled most criteria. Thus, Code[56] established that sufficient histamine is liberated during fatal guinea pig anaphylaxis to account for the death of that animal. Many workers have shown that this species can be protected to a high degree by previous administration of antihistamine compounds.[13,57,58] However, it is notable that although antihistamine compounds vary markedly in their antihistamine activity some such as neo-antergan being much more potent than others

such as benadryl, the same dose of either compound affords protection against anaphylactic shock.[13,58] Again, while the administration of pyribenzamine by aerosol inhalation will protect a large percentage of guinea pigs from the immediate effects of induced anaphylactic shock, Mayer, Brousseau and Eisman[59] remark on the fact that some animals die within twenty-four hours apparently from some other cause. The same dose of pyribenzamine will completely protect these animals against fifteen lethal doses of histamine. The administration of papaverine, while able to protect 53 per cent of guinea pigs from anaphylactic shock, afforded no protection against histamine shock.[60] It is thus apparent that other mechanisms beside histamine release must be participating in this phenomenon. Of considerable interest in this connection is heterophile anaphylaxis. When this antigen-antibody response is produced in the guinea pig with resulting fatal shock, there is no release of histamine into the blood.[61] It should be pointed out that heterophile anaphylaxis is the reverse, in a sense, of foreign protein anaphylaxis and the tissues exhibit signs of greater damage as a rule. However, it is still an antigen-antibody reaction even though in this case the antibody is injected into the guinea pig which possesses naturally occurring antigen.[62] Thus, here is a form of anaphylaxis which seems at present to bear little if any relation to histamine release. It would be interesting to determine the effect of antihistamine derivatives on this reaction.

There is much evidence which supports the theory of histamine release in canine anaphylaxis. In this species, Code[56] has shown that not only is there a marked and explosive increase of the blood histamine but that the major portion is released into the plasma where it is free to exert its characteristic actions. However, if one examines the charts published by Code in his paper on anaphylaxis in the dog, it will be observed that while there is a rapid release of this compound which seems to bear a definite relation to the degree of shock occurring in the early stages, profound shock leading to coma and death in the later stages was observed in the presence of a normal blood histamine. Commenting on this in a later review, Code states,[9] "While histamine seems quite clearly to be the cause of death in the early stages of the reaction, there is some difficulty in incriminating it as the lethal factor when its presence can barely be detected in the blood."

The liver has been regarded as the major site of histamine release in the dog; it has been shown by Ojers, Holmes and Dragstedt[63] that the histamine content of this organ decreases following the production of anaphylaxis in the intact dog. It is also the site of heparin release as demonstrated by Jaques and Waters in 1941.[64] However, it is probable that other tissues participate in the reaction as well for anaphylaxis has been produced in dogs with an Eck fistula[65] as well as in dogs from which the liver has been removed entirely.[66]

Finally, in this species histamine and anaphylactic shock can be prevented in large measure by the previous administration of antihistamine compounds.[67–69] Here again, however, certain discrepancies have been observed. In their observations on pyribenzamine, Yonkman, Oppenheimer et al.[70] noted that, whereas this antihistamine compound prevents histamine-induced bronchiolar constriction in isolated dog lung, the constriction produced by adding antigen to the fluid perfusing isolated lung from a dog previously sensitized was not inhibited. Bronchoconstriction is not a feature, however, of *in vivo* anaphylaxis.

Turning now to the rabbit, one is faced with an apparent reversal of events. It was first demonstrated by Rose and Weil,[71] and later confirmed by others,[72,73] that acute anaphylaxis in this species was accompanied by a drastic decrease in the blood histamine. Furthermore, no consistent increase could be detected in the active plasma histamine. However, the fundamental reaction, namely, release of histamine from cells by antigen-antibody combination, was demonstrated by Katz.[74] Upon the addition of horse

serum to the blood of a rabbit sensitized to this substance, he was able to show that histamine was liberated from the cells into the plasma. This observation, which was confirmed,[75] was then taken as evidence by Dragstedt[76] that histamine plays an active rôle in rabbit anaphylaxis. Dragstedt and his co-workers[72] found that on addition of antigen to blood, which was perfused through the isolated lungs of a sensitized rabbit, histamine was removed from the blood, presumably by the lungs. However, in further experiments, Rose[77] demonstrated that not only was the histamine content of the blood decreased during anaphylactic shock but also that of the tissues, particularly of the lung and spleen. It is perhaps pertinent to note that a marked decrease in the blood histamine of the rabbit can be produced by the injection of glycogen.[78] No evidence of shock accompanies this phenomenon, however, and it is probable that the histamine is taken up in part by the lungs since there is a marked thrombocytopenia at the same time. Providing such histamine remains in the combined or intracellular form in which it is inactive, no effects are produced. This is borne out by the fact that addition of glycogen to rabbit blood *in vitro* does not release histamine from the cells into the plasma.[78] Thus, it appears reasonably clear, as emphasized by Dragstedt,[76] that the fundamental phenomenon in rabbit anaphylaxis again is a liberation of histamine from cells into the plasma. It yet remains to be shown, however, whether antihistamine compounds are capable of inhibiting rabbit anaphylaxis.

In the mouse, anaphylactic shock can readily be produced.[79] In a comparative study on anaphylaxis and histamine intoxication in this species, Perry and Darsie[80] found that while fatal anaphylaxis could readily be induced the animals were quite refractory to histamine intoxication when a dose of approximately 400 mg./Kg. was administered intravenously. Mayer and Brousseau[81] studied the effect of pyribenzamine on these two conditions in the mouse. In controls, the injection of 500 mg. of histamine per body weight killed 50 per cent of the animals used. If either pyribenzamine or benadryl were administered in adequate dosage (10 to 25 mg./Kg.) fifteen minutes before the injection of histamine was made, contrary to expectations, the effect of histamine was enhanced and a dose of 375 mg./Kg. killed 100 per cent. In the mice rendered anaphylactic, on the other hand, some degree of protection was afforded. Both these authors therefore conclude that anaphylaxis in this species is not based on histamine release. Mayer and Brousseau[81] explain their results in histamine poisoning by regarding histamine and the antihistamine compounds as two separate toxins each acting independently. Thus, the toxic action of pyribenzamine or benadryl decreases the amount of histamine required to kill the animals. They further explain the protective action of pyribenzamine in mouse anaphylaxis on some other unknown pharmacologic property of this compound. If one is to consider pyribenzamine as an inhibitor of anaphylactic shock in the mouse on some basis other than its antihistamine property, it is possible that anaphylaxis in other species may in part be inhibited by these antihistamine compounds in a similar way. This may in turn provide some explanation for the disparity between their antianaphylactic and antihistaminic activity. One may conclude from these observations that in all probability the release of histamine is not a factor in this form of anaphylaxis. It may be of interest here to refer to the experiments of Dekanski.[30] He has demonstrated a 100 per cent increase in the histamine content of the skin of the mouse following scalding. Apparently, this excess histamine is formed, not released, as a result of the injury. It would be of interest to know whether any similar mechanism exists in mouse anaphylaxis.

While the rôle of histamine has not been investigated in rat anaphylaxis, it has been shown that thyroidectomy decreases; and the administration of thyroxin increases its susceptibility to anaphylactic shock.[82] Simi-

lar results were obtained in the anaphylactoid reaction to a single injection of egg white in these animals.[82] It is of interest to note that the latter condition can be inhibited by antihistamine compounds.[83]

Finally, there remains the observations of Code and Hester,[84] who found that anaphylactic shock in the horse and calf is accompanied by a decrease in the blood histamine. Andberg, Boyd and Code[85] were able to show that the injection of histamine in the horse produces respiratory symptoms indistinguishable from those associated with acute anaphylaxis in this species. However, other features such as cough and bladder contraction were lacking.

MECHANISM OF HISTAMINE RELEASE FROM CELLS

The older theories of anaphylaxis suggested that the toxic manifestations of this phenomenon might be due to the formation of protein breakdown or cleavage products resulting from proteolytic activity. Although our concept has changed to the more modern one indicating that such a toxic substance must be released and not formed, recent observations would seem to indicate that proteolytic action may indeed play a major rôle in this process. Two theories have been proposed along these lines. In investigating the mechanism whereby venoms are able to liberate histamine from cells, Feldberg and Kellaway[86] found that lysolecithin, a hemolytic enzyme, was formed. They subsequently showed that its formation was responsible for the liberation of histamine from organs perfused with snake and bee venoms.[87–89] It was argued that since cell structure is regarded as a complex of lipoprotein films[90] in which histamine is fixed a splitting of these lipins could account for histamine release. This assumption, however, would have to account for the fact that there is no evidence at present for the existence of a hemolytic effect in anaphylaxis, as pointed out by Feldberg.[7]

Another approach to the enzymatic theory has recently been reinvestigated by Rocha e Silva.[91] In 1909, Biedl and Krause[92] emphasized the marked similarity between peptone shock and anaphylaxis. Lewis[6] and Dale[4] both suggested that protein breakdown might lead to the formation of peptone which in turn might initiate a release of histamine. The observations of Feldberg, Kellaway and O'Connor,[92] and Dragstedt and his co-workers as well as of others, have clearly shown the remarkable similarity between the effects of peptone administration and anaphylaxis. Thus, in the intact dog the injection of peptone causes a release of histamine into the blood,[94] a decrease in the liver histamine,[95] an outpouring of heparin[96,97] and a marked thrombocytopenia,[98] all of which occur in anaphylactic shock as well. Similarly, peptone administration in the rabbit causes a fall in blood histamine[99] and thrombocytopenia. Histamine, furthermore, is released from the white blood cells of the rabbit *in vitro* on addition of peptone.[99] All of these observations, therefore, amply strengthen the concept that the release of histamine and heparin from tissue cells, as well as the thrombocytopenia, are initiated by a similar mechanism in these two types of shock.

Other substances such as animal venoms were shown to produce effects markedly similar to anaphylactic shock as well as to release histamine when injected into animals.[100,101] In considering these effects, Rocha e Silva[101] concluded that this property could best be explained by the fact that these venoms contain a proteolytic enzyme similar to trypsin since trypsin itself was able to produce effects indistinguishable from those of venoms. Further investigation by Rocha e Silva[102] and Arellano, Lawton and Dragstedt[103] showed that trypsin was capable of producing many of the alterations in blood histamine in different species similar to those occurring in peptone and anaphylactic shock.[103–107] While there are definite discrepancies, such as the failure of trypsin to release histamine in the guinea pig,[106,108] heparin in the intact dog[109] or the inability of benadryl to prevent the symptoms of trypsin shock in the dog or the guinea pig,[110] Rocha e Silva believed

that the evidence was sufficient to warrant a further search for a trypsin-like enzyme in anaphylaxis.

Pursuing this idea, he and his co-workers demonstrated that in the isolated dog liver perfused with tyrode solution trypsin alone was capable of releasing histamine whereas peptone, ascaris extract or antigen required blood as the perfusing medium.[105,113] Using blood preserved by the silicone method of Jaques et al.,[111] by means of which it may be kept from coagulating for several hours without deterioration of any of its constituents, relatively enormous quantities of histamine and heparin were released from the isolated liver on addition of peptone. These surprising results made it obvious that whereas trypsin, a proteolytic enzyme, is capable of releasing histamine and heparin from the isolated dog liver in the absence of blood the latter, or one of its constituents, is essential for the release of these substances when peptone, ascaris extracts or antigen (in the sensitized liver) is used.

The marked reduction in platelets and leukocytes which accompanies all these reactions both in the intact animal or when isolated liver is perfused with blood[112,114,115] was taken as evidence of their participation in the mechanism of histamine release. By making stained smears of liver tissue the platelets could be demonstrated within the parenchyma. It was shown that the degree of disintegration of these elements bore some relation to the quantities of histamine and heparin released. Thus, in the earlier experiments when heparinized blood was used as the perfusing agent sometimes little or no histamine was released and the platelets were found intact. With silicone blood, the platelets were found to be disintegrated and there was an accompanying enormous release of histamine and heparin.[91,112] Since platelets are known to contain kinase for plasma trypsin,[116] Rocha e Silva and Texeira[117] have formulated the theory that their disintegration activates a proteolytic enzyme, most probably trypsin, which in turn causes cell damage and release of metabolites such as histamine and heparin. In further support of this attractive theory, Jaques, Rocha e Silva and Scroggie[119] have demonstrated that plasma trypsin, or an enzyme like it, is activated in the dog liver perfused with silicone preserved blood to which peptone is added. Thus, fibrinolysis of the clot, which forms in the perfusate when protamine is added to inhibit the action of released heparin,[117] was found to occur. Finally, soybean tryptic inhibitor which prevents the action of trypsin was also found to inhibit this fibrinolysis. Although these experiments have not been repeated for antigen-antibody reaction, they constitute a great step forward in our understanding of the mechanism of peptone shock in the dog and may shed more light on the mechanism of histamine release in anaphylaxis in other species.

Additional support of the theory that a tryptic ferment is responsible for histamine release has been furnished by Rocha e Silva.[120] He observed that papain, a mixture of proteolytic enzymes with some of the specific characteristics of animal cathepsins, is capable of releasing histamine by virtue of its ability to split benzoyl-l-argininamide. This is a specific substrate for cathepsin II[121] as well as a typical one for trypsin. Rocha e Silva[10] has therefore suggested that histamine is held in the cell forming an amide linkage with either lysine or arginine. Synthetic compounds of histamine, chemically bound to amino acids by a peptide linkage, were prepared and suggested as chemical models of tissue histamine. These compounds were pharmacologically inactive but upon acid hydrolysis which ruptured the peptide bond the amine was liberated in active form.[122]

That protein breakdown occurs during anaphylactic shock in the dog has recently been shown by Miller.[52] This cannot be regarded as a specific result of anaphylaxis for it is known to occur following many other forms of injury.[123,124] Yet it supports the proteolytic theory of antigen-antibody combination. It is obvious, however, that by whatever basic mechanism histamine and other metabolites are released in an active

form in most types of anaphylactic shock. Whether a transient increase or decrease in the blood histamine occurs would seem to be less important and is simply an indication of shift of histamine from one locale to another. Of greater importance is whether during this shift it is released and how sensitive are the tissues with which it comes into contact. As will be pointed out, there is evidence to show that in the allergic or hypersensitive state certain tissues are much more reactive to histamine than when they are in the normal state.

As in many other aspects of physiology there are species differences in anaphylaxis. The fundamental reaction of a release of histamine from cells by the interaction of antigen with antibody has, for the most part, been substantiated. As Code[9] rightly points out, the challenging problem is the damaged cell. While the injection of histamine may reproduce some of the symptoms of anaphylaxis, it is not capable of producing the morphologic changes which result from anaphylactic shock.[7] If present, it is released along with other substances as a result of this damage. That histamine plays a major rôle in this syndrome is beyond question and, as will be seen in another section of this symposium, confirmatory evidence, although it is of an indirect nature, is ample through the effect of antihistamine compounds.

RÔLE OF HISTAMINE IN ALLERGY

The basic factors involved in the mechanism of both allergy and anaphylaxis have led many to believe that they are manifestations of one and the same phenomenon. As will be seen, this aspect of the field has not kept abreast of the evidence for the participation of histamine in anaphylaxis.

At the outset, it should be remembered that whereas acute anaphylaxis is a general reaction in which many of the body tissues participate, allergic phenomena are usually confined to one or two specific tissues such as the mucosa of the upper respiratory tract, the bronchiolar musculature and glandular tissue or the skin. While it is possible that a marked increase in the blood histamine may occur in serum anaphylaxis in man or in constitutional reactions following the injection of too large a dose of pollen extract, such determinations do not appear to have been made.

The first presumptive evidence for a release of histamine in allergy was reported by Lewis and Grant.[125] They observed that the wheals produced by stroking patients with sensitive skins contained a substance with some of the pharmacologic properties of histamine. It was not, however, until Barsoum and Gaggum[33] published their method for the extraction of histamine in the blood that any quantitative studies were attempted. There followed a few reports indicating that the blood histamine was increased in patients who had asthmatic attacks.[126–128] Following the modification of the method by Code,[32] he and MacDonald[34] noted that the histamine content of the blood of normal (non-allergic) individuals remained remarkably stable and these results were confirmed by Rose.[45] MacDonald and Haworth[129] then studied a group of asthmatics and could find no significant change in the blood histamine during attacks as compared to quiescent periods. Similar results were later reported by Rose[130] on a larger group of patients. In contrast, Randolph and Rackemann[26] noted that the blood histamine was increased in some of their asthmatic patients during attacks. Since that time we have made many determinations of the blood histamine in patients with asthma, both in and out of attacks, without observing any correlation between the histamine content of the blood and the appearance of symptoms.[131] As often as not, the blood histamine level was decreased during attacks as compared to quiescent periods. Studies on the blood histamine in patients with hay fever have yielded similar equivocal results.[130,131] More significant perhaps are the observations of Myrhman and Tomenius[134] who were able to show a marked increase in the histamine content of the stools of asthmatics as compared to those of normal subjects.

The sputum of asthmatics is said to contain histamine[137] and it has recently been found in the nasal secretion of patients with the common cold and rhinitis.[132]

Evidence of a more direct and convincing nature has been obtained in the studies on allergy and other conditions of the skin. Marked variations in the histamine content of the blood were observed in patients with urticaria, angio-edema and chronic eczema.[130] In the former two a decrease was noted with the onset of symptoms and wheal formation whereas in eczema the histamine content of the blood was often found to be increased. Wide fluctuation in the blood histamine, however, did not seem to be related to the remissions or exacerbations at the time. By assaying the histamine content of the skin directly on biopsy material, Pellerat[17] has shown that a decrease occurs following burns or freezing by ethyl chloride. The increase of histamine in the blood of patients following burns has been previously noted.[139,140] The skin histamine was also decreased in various skin lesions of an allergic or other nature while the blood histamine was increased. Katz[141] has shown that histamine is liberated from the skin of allergic patients when wheals are produced by the intradermal injection of antigen. On the other hand, Abramson and his coworkers[142] were unable to detect histamine in similar wheals by the sensitive method of reversed iontophoresis.

The relationship of histamine to dermatographia was indicated by Kalk[133] who showed that following the production of wheals in sensitive patients one could detect the release of free HCl in the stomach. Similar findings were reported by Horton, Brown and Roth[135] in patients with hypersensitivity to cold and, as a result, they attributed the systemic reactions observed to a general release of histamine into the circulation. The first direct estimation of blood histamine in physical allergy was made by Capps and Young[136] who showed an increase in the blood histamine of a patient with photosensitivity following exposure to ultraviolet light. In earlier studies, Rose[35] was able to show a transitory increase of the peripheral blood histamine in five of ten patients with dermatographia following the production of whealing and in two of three patients with cold sensitivity following the application of cold. In a recent more detailed study of two patients with hypersensitivity to cold these observations have been confirmed and somewhat amplified.[138] It was found that these clinically indistinguishable patients differed basically in that in one the symptoms were due to histamine release whereas in the other some other metabolite must have been involved. These conclusions were based in one of these patients on a release of histamine into the plasma following exposure to cold, reproduction of symptoms by histamine injection and complete inhibition of symptoms by the administration of antihistamine compounds. In the other none of these findings could be substantiated although exposure to cold resulted in the production of intense symptoms. In this connection, Peters and Silverman[143] studied a case of heat allergy and concluded that acetylcholine was probably the substance which mediated the reaction although they did not exclude histamine. These findings may explain the discrepancy in the results obtained by treatment of such patients with antihistamine compounds as reported by others.[140]

In an attempt to explain the divergent findings of a normal high or low blood histamine level in patients with allergic manifestations, Rose[138,145] observed the effects of both the subcutaneous and intravenous injection on histamine on the blood histamine level. It was first observed that general changes in the peripheral circulation, associated with flushing of the face and neck, were common to all subjects whether allergic or not. Allergic manifestations, such as the production of transient asthma, urticaria, changes in the nasal mucous membrane or production of headaches, could be produced only in those patients who actively suffered from such complaints. Thus, râles and difficult breathing were

noted only in asthmatic subjects. Such observations have been reported many times previously, notably by Weiss, Robb and Ellis.[146] The most recent contribution to this field is the interesting set of papers by Curry. He has observed that whereas the administration of histamine to normal subjects produces little or no effect on the vital capacity, a marked reduction occurs in the pulmonary vital capacity of patients who suffer from asthma following this procedure.[147,148] Antihistamine compounds administered one hour beforehand could completely inhibit this effect.[149] Rose[145] has further shown that in man the symptoms of histamine administration can be produced without an increase in the blood histamine. During the intravenous administration of this compound, the total blood histamine may actually decrease. Such findings are not surprising when compared to the results obtained in burn or traumatic shock in man,[140,150] the changes which occur in rabbits[77] and horse and calf anaphylaxis.[84] In the acute stages of all these phenomena the blood histamine is lower than normal.

Reference must again be made to the state of histamine in the blood. Since the bulk of the blood histamine is contained within the white cell elements and since in this form it is inactive, an increase in this component of the blood histamine need not signify activity. Code and MacDonald[34] showed that the blood histamine can be markedly increased in patients with certain blood dyscrasias. In studies on the relation of the blood histamine to the cellular compounds of the blood in man values of 1,000γ/100 cc., nearly 500 times more than normal, have been found in patients with myelogenous leukemia.[138] Such patients are neither in shock nor allergic. Yet if this amount of histamine were suddenly released, one can readily imagine the dire consequences when it is known that as little as 7 gamma of base injected intravenously can lower the blood pressure anywhere from 15 to 80 mm. of Hg.[151]

The demonstration by Katz and Cohen,[115] that the addition of antigen to the *in vitro* blood of patients suffering from hay fever or asthma causes a sudden release from the cells into the plasma, is of fundamental importance. This is the counterpart of *in vitro* anaphylaxis as originally shown by Katz[141] on rabbit blood. The effect of the administration of antihistamine compounds on the symptoms of various forms of allergy will be found reviewed in another section. Their ability to inhibit to a large extent the symptoms of hay fever and urticaria[153,154] is not as evident in the treatment of asthma.[155,156] That this may be a question of dosage seems possible according to McGavack et al.[50] However, certain aspects of their activity are pertinent. It should be noted that they may inhibit other substances such as acetylcholine, as well as hyaluronidase, as recently demonstrated by Mayer.[157] The implications of this latter observation are obvious when the activity of hyaluronidase as a "spreading factor" is recalled. Thus, these compounds do not provide absolute proof that the substance inhibited is histamine. Even the itching of various skin lesions, which seems to be so effectively controlled in the majority of instances, can be attributed to their anesthetic quality which is three times as potent as procaine.[158]

Of considerable interest is the work of Ahlmark[159] who has demonstrated a marked increase in the histaminase content of the plasma of women during pregnancy. He has shown that whereas little or no activity exists in the plasma of man or non-pregnant women there is a marked increase in pregnancy which reaches its peak by the seventh month. These results have recently been confirmed by Rose et al.[160] Although the significance of this marked increase in plasma histaminase is not understood, since there is no alteration of the blood histamine during pregnancy,[161] it may have some bearing on the frequent observation that women suffering from any of the common allergic manifestations, such as asthma, hay fever or eczema, are often freed of their complaints when they become pregnant.[162] Here again it must be remembered that plasma cholinesterase is increased as well[163]

and in this connection Curry[148] has shown that the tracheobronchial tree of patients with asthma is even more susceptible to the effects of mecholyl chloride than to histamine.

Much attention has recently been drawn to the possible allergic nature of demyelinating diseases of the central nervous system.[164–166] On this basis histamine has been advocated as a therapeutic agent in the treatment of disseminated sclerosis.[167] It should perhaps again be pointed out that while tissue damage of a permanent nature, with associated morphologic changes, may arise from antigen-antibody reaction, these changes do not result from the administration of histamine itself. That tissue lesions based on antibody-antigen reaction may occur in man is suggested by the recent work of Cavelti.[152] However, the basic mechanism of such damage is still obscure and it must be reiterated that the release of histamine, if and when it occurs, is the result and not the cause of such damage.

In summary, it seems evident that two factors must be operative in patients with allergic disease with reference to histamine effects. These are: first, that the tissues must be hypersensitive to histamine and secondly, that there must be a shift of this substance from the intracellular or inactive form to the extracellular or free state. If this occurs in a local area of skin or mucous membrane, the amount of histamine released could hardly produce an increase in plasma histamine without causing systemic effects. When large amounts are liberated suddenly into the plasma, as in certain cases of hypersensitivity to cold, systemic effects become manifest. It should be noted, however, that such an increase is very transient in nature because of the rapid removal of histamine by body mechanisms. It seems probable that small amounts of histamine may be continually released in some cases of allergy, producing local symptoms, and rapidly removed from the blood by means of kidney or intestine as evidenced by the increased histamine content of urine and feces under these conditions. A marked increase in the total blood histamine without alteration of the plasma histamine is completely compatible with absence of symptoms.

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The Antihistaminic Drugs*

Pharmacology and Therapeutic Effects

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THE rapid developments in the field of antihistaminic drugs have resulted in enough confusion and misunderstanding to justify an attempt to summarize and evaluate the various phases of the subject. This paper consists of an evaluation of the essential experimental findings as well as clinical experiences with a number of antihistaminic drugs, some of which are already available to the general medical profession and one or two others which are still in the trial stage at the time of this writing. Although this presentation will cover the work of other authors as fully as possible, it will stress mainly my own clinical and experimental experience.

HISTORICAL BACKGROUND

The histamine theory for the mechanism of anaphylaxis proposed by Dale and Laidlaw[1] and the concept of histamine release in the allergic reaction suggested by Lewis and Grant[2] have been corroborated and amplified by many experiments. Even though there are evident reasons to justify the belief that some of the manifestations of allergy and anaphylaxis cannot be explained by histamine alone, there is almost unanimous agreement that histamine plays a prominent rôle in the phenomena of hypersensitiveness. This realization has led in recent years to a concerted effort to find substances antagonistic to histamine.

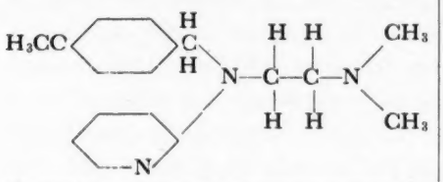
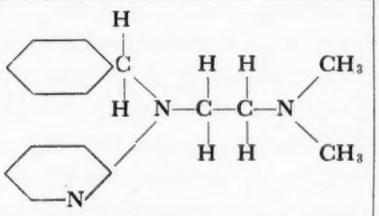
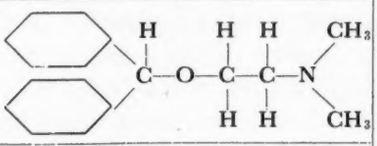
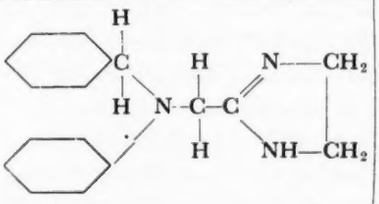
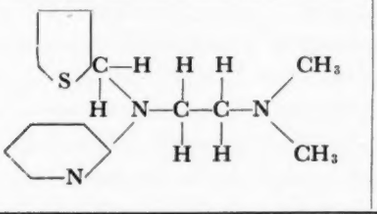
The amino acids, particularly histidine, cysteine and arginine, were among the first effective antihistaminic and antianaphylactic materials.[3] However, the ratio of their toxicity to their efficiency was so great as to make their use impracticable. In 1933, Fourneau and Bovet[4] reported that certain of their series of synthesized phenolic ethers had the ability to counteract the action of histamine *in vivo* and *in vitro*. This was the impetus for the production of a series of such compounds. Among the most promising of these were thymoxyethyldiethylamine (929F)[5] and N-phenyl-N-ethyl-N′diethylethylenediamine (1571F).[6] These compounds, however, were also too toxic in proportion to their antianaphylactic and antihistaminic activity.

The efficacy of the ethylenediamine radical in 1571F was recognized and there began a further series of syntheses and trials of chemicals containing this radical. These efforts finally resulted in the first drug sufficiently effective to be used clinically, N′phenyl-N′benzyl-N-dimethylethylenediamine, or antergan (2339RP).[7] This drug was first used clinically in France and found to be effective in the symptomatic relief of many allergic manifestations. The ratio of therapeutic efficiency to toxicity in antergan was still not sufficiently favorable.

CHEMISTRY OF MODERN ANTIHISTAMINICS

Although I shall stress the experimental and clinical findings of the drugs at present on the American market (benadryl and pyribenzamine), I shall also briefly speak about others which are available outside of this country and of one or two others which shortly may be available here. The names and structural formulas of these drugs are as follows:

* From the Department of Medicine, Division of Allergy, Northwestern University Medical School, Chicago, Ill.

Structural Formula	Chemical Name	Trade Name	Manufacturer
	N-*p*-methoxybenzyl-N-dimethyl-aminoethyl-α-aminopyridine	Neoantergan	Rhone-Poulenc Co. Paris, France
	N′pyridyl-N′benzyl-N-dimethylethylenediamine	Pyribenzamine	Ciba Pharmaceutical Products, Inc. Summit, New Jersey
	β-dimethylaminoethyl benzohydryl ether	Benadryl	Parke, Davis & Co. Detroit, Michigan
	2-(N-phenyl-N-benzyl aminoethyl)-imidazoline	Antistine	Ciba, Basle Basle, Switzerland
	N-(2-pyridyl)-N-(2-thenyl)-N′, N′-dimethylethylenediamine	Thenylene (Abbott) Histadyl (Lilly)	Abbott Laboratories North Chicago, Ill. Eli Lilly & Co. Indianapolis, Ind.

EXPERIMENTAL AND PHARMACOLOGIC

The pharmacologic effects in animals and man are quite the same with each of these drugs although they may differ quantitatively in individual activities.[8] The status of their comparative activities is, however, in confusion because of the tendency for experimenters to vary their experimental technics both qualitatively and quantitatively. I shall therefore refrain at this time from emphasizing quantitative differences between these drugs and shall limit my discussion chiefly to their major similarities.

Antihistamine Action. Any one of these drugs administered to animals such as guinea pigs, dogs and cats is capable of preventing fatal shock from histamine when injected intravenously. One type of experiment consists of noting the number of lethal intravenous doses of histamine tolerated by guinea pigs after a fairly large dose of the protective drug is given intraperitoneally. In such an experiment, for example, we found that 3 mg. of the drug per Kg. of animal protected against five lethal doses of histamine with benadryl, thirty-seven with pyribenzamine and 125 with neoantergan. We soon learned, however, that such comparisons do not give an accurate conception of the efficacy of the drug. Such tremendous doses of histamine are far removed from the probable amounts released during anaphy-

laxis and the allergic reaction. The action of these drugs in preventing fatality from one lethal dose of histamine was regarded as more closely approximating physiologic conditions. On that basis we found[9] that the difference between such drugs as benadryl and neoantergan was not nearly as striking.

Prevention of Bronchospasm from Aerosolized Histamine. The inhalation of aerosolized histamine by guinea pigs produces bronchospasm and dyspnea which progress to convulsions and death if exposure is continued. The prevention of these histamine effects by the prior administration of a protective drug has been utilized as a measure of antihistamine activity. Unfortunately, the technics of the various experimenters differ in many respects.[10–14] The route, dose and time of administration of the protective drug, as well as the concentration of histamine, time of exposure and details of administration may vary radically. Even the end point differs materially. Many take death as the criterion, others convulsions and still others the first evidence of unquestioned dyspnea. For these reasons it is hardly ever possible to make fair comparisons of the efficiency of these actions of different drugs as reported by different experimenters.

Nevertheless, the experience of others as well as our own indicates that judged by such general methods both pyribenzamine and neoantergan are highly effective in preventing bronchospasm. We have performed similar experiments using dyspnea as an end point and administering the protective drug not only by the usual route but by inhalation. These experiments were carried out with a wide variety of antihistaminic drugs and the details will be published elsewhere. We shall confine ourselves here to the drugs under discussion. Pyribenzamine and neoantergan were of a high order of efficiency in the prevention of dyspnea due to aerosolized histamine. Benadryl, the thenyl compound and antistine showed definite protection but not as marked as was obtained with the other drugs.

Histamine Contraction of Intestinal Strip of Guinea Pig. If an antihistaminic drug is added to the bath in which a piece of guinea pig ileum is suspended, the contraction normally produced by histamine will be prevented by the addition of the antihistaminic agent. All drugs of the type described are capable of producing this effect.[11,14–17] We have utilized this method quantitatively in a comparative study of a large series of drugs. The findings with all of these drugs and a critique of the method will be given elsewhere. We may state here that of the drugs considered in this paper, pyribenzamine and neoantergan were the most effective, that is, the least concentration of the drug was required to inhibit contraction produced by a standard amount of histamine. The other drugs, however, also showed a high degree of this property. Contractions produced by other spasmogenic substances, i.e., barium chloride or acetylcholine, were prevented to an appreciable extent by benadryl; the other drugs had only slight inhibitory effect.

Antiwhealing Properties. In most types of allergic manifestations localized edema as a result of capillary permeability changes is the most characteristic phenomenon. Since a histamine wheal can readily be produced in the skin of man, it was thought that observations on the inhibition of wheals produced by histamine and other whealing agents might throw light on the potency of the drugs and their possible mode of action. By applying solutions of these drugs to scratches of the skin either prior to or in combination with the application of histamine, we were able to show[18] that these drugs inhibit whealing due to histamine. By varying the histamine concentration in a series of scratches while keeping the antihistamine concentration constant or by reversing the procedure, we were able to arrive at an approximation of the potency of this antiwhealing effect. Elsewhere we shall discuss in detail the data obtained by comparative studies of this phenomenon with a large series of drugs. At present suffice it to say that the drugs discussed here were all active in this respect. In addition we found that the wheals produced by antigen-anti-

body reaction, codeine and similar substances, were also inhibited. Last and Loew,[19] in studies with benadryl and neoantergan on capillary permeability in rabbit skin, found that these drugs prevented or diminished the action of injected histamine but did not inhibit other agents causing increased permeability. I would suggest that this discrepancy may be due to the fact that rabbit skin is not as suitable as human skin for such studies.

Other Properties of Histamine. These drugs will combat the depressor effect of histamine on the blood pressure of the cat or dog. Although such observations are not complete for all drugs, none of the drugs studied from this viewpoint showed any ability to inhibit the histamine function of stimulating gastric secretions.[20] As a matter of fact, Halpern has pointed out[21] that when guinea pigs survive histamine shock from very large doses of histamine (300 MLD or more) by virtue of being subjected to large doses of the antihistaminic drugs, they are apt to develop acute perforating gastric ulcers in twenty-four to forty-eight hours. I have been able to corroborate this finding. The presumptive explanation is, of course, that this particular function of histamine, the stimulation of gastric secretion, is not inhibited by the antihistaminic drugs, thus allowing the excess histamine to produce gastric hypersecretion and an acute ulcer. It should be noted that McGavack and his associates[22] claim that gastric secretion in man is depressed by benadryl. As time progresses we may find a number of functions of histamine which the so-called antihistaminic drugs are unable to combat.

Antianaphylaxis. The drugs under consideration have been found effective in the prevention of anaphylactic shock in guinea pigs and other laboratory animals.[11,15,23,24,25] Our experience indicates that these drugs differ much less in this property than in their antihistaminic action. The antianaphylactic effect could also be demonstrated on the sensitized guinea pig ileum *in vitro*. In our preliminary work[9] it was indicated that less drug was required to inhibit an anaphylactic contraction than a histamine contraction of similar magnitude. Such a finding would tend to cast some doubt on the concept that histamine release is responsible for the anaphylactic contractions. However, more extensive experience indicates that the variations in the anaphylactic contractility of various segments of the ileum of the same animal are so great that any conclusions based on the activity of different strips may be questioned.

Other Pharmacologic Actions. The drugs under discussion here (and other antihistaminic drugs) have a local anesthetic action. It is suggested by some that it is this local anesthetic action which is responsible for the relief of pruritus and possibly for other histamine effects. That this explanation is doubtful is indicated by the relatively small doses required for antiallergic effects as compared with the local analgesic action. These drugs are similar in that in small doses (in man) they produce sedation while with fairly large doses excitation is produced in animals and also in man.

The toxicity of these drugs has been investigated in various species of animals. In general, one may say that there are no striking differences between the drugs in toxicity studies although there is considerable variation in their sedative action in man. It is established that the present series of drugs and most of the other new ones have much more favorable antihistaminic toxicity ratios than the amino acids or the early synthetic antihistamine compounds. Chronic toxicity studies in animals have thus far been practically negative.

CLINICAL

Considerable confusion exists with regard to the clinical action and function of the antihistaminic drugs. It should be clearly understood that they are solely palliative forms of medication. A dose of the drug may be effective for several hours, frequently only for two hours. Most observers agree that there is no tendency for cumulative effects or persistence of action after the drug has been discontinued, even after a pro-

longed period of administration. It is absolutely futile to have a patient take such a drug for weeks or days or even hours preceding an anticipated allergic episode such as seasonal hay fever. As a matter of fact, such abuse of this therapy may do harm because tolerance to the drug may result from long continued use.

The action of these drugs is limited. They do not correct all of the manifestations of histamine or allergic action nor do they relieve any particular symptom completely. For example, the stimulation of gastric secretion by histamine is not inhibited, asthma is very little affected and many types of allergic manifestations are not benefited. Even in allergic phenomena in which the drug works well, urticaria or allergic rhinitis for example, 100 per cent inhibition of the lesion or symptom is practically unknown. The histamine antagonists are most efficacious in the patient who is on allergic management when the drug is made to serve as an aid to allergic therapy rather than as a substitute for it. The need for avoidance of allergens cannot be replaced by drug therapy nor are the antihistaminic agents substitutes for the more complete and lasting tolerance possible by desensitization. Antispasmodics, vasoconstrictors and expectorants are still important remedial agents, sometimes as adjuncts to the histamine antagonists and at other times superior to them.

Hay Fever and Perennial Allergic Rhinitis. Last year I reported on a series of 254 seasonal hay fever patients of whom 82 per cent received benefit from pyribenzamine and on 130 patients with perennial vasomotor rhinitis of whom 64 per cent were helped.[26,27] Our subsequent experience has been about the same. Others[28–31] have reported comparable results. Our experience with neoantergan[26,32] in various types of allergic rhinitis was also satisfactory but not quite as good as with pyribenzamine. Bovet and his associates[33] report excellent results with neoantergan. Benadryl was also of help in these cases but the incidence and degree of relief were considerably less than with the other two drugs. Some workers have claimed[34,35,36] better results from benadryl than I have been able to obtain; one author[31] has claimed results superior to those obtained with pyribenzamine. Our experience in the past year with antihistaminic compound histadyl, known as thenylene by another manufacturer, indicates that it also is a potent and useful drug in these conditions. Antistine is also of benefit in some cases[37,38] but is much less consistent in its action than the other drugs.

These five drugs, as well as the other histamine antagonists not discussed here, display individualistic behavior toward patients. Perhaps it would be even more correct to say that each patient is individualistic in his behavior toward these drugs. One patient may benefit from drug A and not from B; the next patient may show an exactly opposite response. As a matter of fact, sometimes a drug of very low general efficacy may prove to be the best drug for a particular person.

As I have pointed out previously, the benefit derived in any one type of allergic ailment is limited. In allergic rhinitis the most marked result is in diminution of the hyperesthetic symptoms, itching and sneezing. The coryza is also pretty well controlled. The intranasal edema, however, responds less readily both in frequency and degree. One notices very often that the early symptoms of hay fever may be well controlled whereas the late congestive stage may not be benefited as much. Perhaps the greater resistance to antihistaminic therapy shown by perennial cases is due to the fact that nasal obstruction is apt to be a more marked feature in this type of allergic rhinitis.

In the more or less continuous phases of allergic rhinitis the drug should be used three or four times daily, usually in 50 mg. doses in the adult. When the symptoms are irregular, it is best to take the medication as needed and repeat in four to six hours if necessary. When the symptoms are confined to the morning hours, a dose of the drug on arising or after breakfast will suffice. In a good many patients, taking the

medication at bedtime may result not only in a better night but frequently in a better morning. The combination of ephedrine with the histamine antagonist may produce greater effects, particularly on nasal blocking. When sedation from the antihistaminic becomes objectionable, the addition of a cerebral stimulant such as amphetamine or desoxyephedrine may solve the difficulty. I have found, however, that in most instances I could solve this problem even better by substituting another type of antihistaminic drug. Since in some individuals these drugs produce excessive dryness of the throat, measures to combat the latter may be necessary.

In speaking of benefit from these drugs the statistics refer, of course, only to the number of persons helped and do not indicate the extent of benefit derived. The percentages are impressive but the degree of relief in many instances is far from satisfactory. The mild cases are helped more readily. By the same token, those whose hay fever has been partially improved by desensitization are more likely to obtain worth while effects from the antihistaminic drugs.

Asthma and Allergic Cough. Asthma does not respond well to these drugs[27,33,36,37,38] although more favorable results are reported by some authors.[22,39,40,41] In a small percentage they are of some benefit but the degree of relief does not approach that obtained with the usual antiasthmatic drugs (ephedrine, epinephrine, aminophylline and iodides). The irritative preasthmatic or allergic cough responds more readily than the dyspnea and in this regard the action of these drugs may be better than that of the old antiasthmatic remedies. Children show a greater tendency to benefit than adults. At times, the combination of an antihistaminic drug with ephedrine or aminophylline, or both, may prove to be effective. I have noted a general misunderstanding among many physicians concerning the efficacy of these drugs in asthma. Very frequently I see patients with asthma who have been previously dosed with benadryl or pyribenzamine for weeks or months without relief whereas a day or two of medication with the old antiasthma remedies quickly produced the desired result. In those patients who have asthma with their hay fever the latter may be strikingly benefited while the asthma is not affected. Since such associated asthma is effectively prevented by pollen desensitization, this constitutes a valid reason for not depending on the antihistaminic drugs in hay fever.

It is not clear why asthma should be so refractory to the antihistaminic drugs. One possible reason is that we may be dealing with a chemical mechanism in asthma which differs from that in hay fever. Another possibility is that the bronchial tissues may release a much greater concentration of histamine so that the amount of drug tolerated orally is insufficient to combat it. For this reason I have experimented with aerosols of antihistaminic drugs, particularly pyribenzamine. Although the technical problems are not entirely solved, it would seem possible not infrequently to obtain prompt relief with such therapy.

Urticaria, Serum Sickness and Dermographism. Pyribenzamine and benadryl have been about equally effective in the symptomatic improvement of urticaria.[26,29,42–45] In approximately 80 per cent of patients with urticaria and angioneurotic edema worth while relief of the discomfort of itching is obtained. The edema is also diminished in many cases but not as consistently or as completely as the itching. In the serum sickness type of reactions consisting of urticaria or angioneurotic edema, arthralgia, fever and other symptoms occurring several days after the administration of serum, penicillin or sulfonamides, these drugs are also effective. The joint symptoms in these patients are, however, more resistant to palliation than the tissue edema. The acute urticarial dermatoses appear to respond better to antihistamine medication than the chronic. In severe cases the drug is required every three or four hours and large doses, such as 100 to 150 mg., may be necessary. In such instances pyribenzamine has the advantage

because larger doses are usually better tolerated than benadryl. The thenyl compound and neoantergan[32,33,46] have also been effective in these conditions. Good results have also been claimed for antistine[37,38,47] but in our experience its effectiveness is not dependable. There is no evidence whatever to indicate that any of these drugs shorten the course of the urticaria or serum sickness.

One of the first clinical conditions in which the antihistaminic drugs were used was dermographia.[48] The improvement in itching and welting prompted us to try these compounds as prophylactic medication prior to the performance of specific skin tests in allergy studies of those patients whose dermographism prevented accurate interpretation of the tests. This was successful in the majority of such patients. One or two doses of the drug taken orally one hour and three or four hours prior to the performance of the tests eliminated most of the skin irritability while interfering very little with the specific skin response to the antigen. It is important, however, to keep in mind that such premedication might conceivably inhibit mild skin reactions sufficiently so that they become negative.

Atopic Dermatitis and Other Types of Dermatitis and Pruritus. The itching of atopic dermatitis (flexural eczema, infantile eczema, neurodermatitis) has been helped materially in most patients by the oral use of antihistaminic drugs.[26,28,29,30,33,44,45,47] While usually only the itching is influenced, it happens not infrequently that discontinuance of the scratching may result in improvement of the skin condition. In many instances the drug is required only at night. When sedation is of advantage, benadryl may act more favorably than pyribenzamine. On the other hand, because of its greater sedative action, benadryl can rarely be used in ambulatory patients when large doses are required. Although there is individual variation in response to the different drugs, benadryl and pyribenzamine produce about the same incidence of relief. Neoantergan and the thenyl compound are also effective. It should be clearly understood that a goodly number of patients fail to obtain any degree of relief from these drugs.

The itching of contact dermatitis was helped in some instances but not as frequently as in atopic dermatitis. In dermatophytosis, eczema of the hands and itching dermatoses of unidentified types relief was sufficiently frequent to justify a trial of these drugs. Pruritus ani and pruritus vulvae were benefited in most instances by pyribenzamine. In a few cases in which we tried benadryl, neoantergan and the thenyl compound similar relief was obtained. In other types of generalized pruritus there was occasional relief but in most of them, contrary to the experience of some other workers, no benefit was obtained.

Since we had shown[18] that antihistaminic drugs applied locally inhibit the wheal and itching of histamine or the specific antigen, it was believed that topical application of such a drug as pyribenzamine might be useful in itching dermatoses. After considerable experimentation with solutions, emulsions and ointments of various concentrations we finally decided that a 2 per cent ointment of pyribenzamine hydrochloride in a water-washable ointment or a similar strength of pyribenzamine base in a petrolatum material was the most useful. Such ointments applied locally not only may augment the effects of the drug given orally but may even be effective at times when the latter fails. This topical therapy[49] has been most useful in atopic dermatitis, particularly when the lesions are not too acute. Such therapy should not be used when the skin is raw or weeping. The ointment has been very helpful in a number of instances of pruritus ani. In other types of dermatoses with itching benefit was also obtained but not so regularly.

Miscellaneous Conditions. The data on gastrointestinal allergy are meager. My own experience indicates that these drugs may help or prevent such manifestations but not in all instances by any means. McGavack and his associates[22] report relief of two cases of spastic colon and nine of functional

dysmenorrhea by the use of benadryl. My experience with migraine has not been very encouraging although some clinical reports present favorable results. I have seen the pruritus and the edema of a patient with dermatomyositis materially helped by pyribenzamine. There has been some claim[22] that cardiac asthma has been improved in some instances. Other conditions in which some degree of benefit has been claimed are insect bites and erythema multiforme. The itching and edema of a marked local reaction from the injection of a specific antigen during desensitization therapy can be benefited by a dose of one of the drugs. In the prevention of systemic reactions from desensitization therapy a 50 mg. dose of pyribenzamine or similar drug taken thirty to sixty minutes prior to the injection may prevent the reaction and allow increments in antigen doses not otherwise possible. In my experience, however, this action is only moderately quantitative, that is, it is not sufficiently great to prevent reactions from excessive dose increments.

ADMINISTRATION AND DOSAGE

The antihistaminic drugs are generally administered orally, in the form of tablet, capsule or liquid. The usual dose for adults is 50 mg. A few patients respond to smaller doses while some require 100 or even 150 mg. The large doses are not as well tolerated with benadryl as they are with pyribenzamine. Antistine requires larger doses than the other drugs. The dosage of benadryl or pyribenzamine in children under ten is 25 mg. but 50 mg. doses may be used if the smaller amounts are ineffective. For infants we usually give 10 to 20 mg. in the form of an elixir.

The frequency of administration depends on the allergic manifestation and its behavior in the individual patient. For example, if the itching of atopic dermatitis is troublesome only at night, a dose of the drug at bedtime is sufficient. If the allergic rhinitis manifests itself only for a couple of hours in the morning, medication on arising would be indicated. Frequently I have noted that a dose of medicine at bedtime may prevent the severe sneezing spell in the morning. When the symptoms are more or less continuous, three or four daily doses and sometimes even more are required. At times, the addition of ephedrine, aminophylline or both may be of synergistic help particularly in asthma. If the antihistaminic drug produces marked sedation, it may be combined with the above drugs or with dexephedrine or benzedrine.

Benadryl can be given intramuscularly in doses of 10 mg. or more. Benadryl, pyribenzamine and antistine have been administered intravenously. Such modes of administration are seldom indicated and when considered advisable should be used cautiously.

I have already referred to other forms of administration: ointments, which may be of help in itching dermatoses and aerosols of pyribenzamine, which may be of aid in some instances in the relief of the allergic cough. Antistine has also been used in eye drops.

UNDESIRABLE ACTIONS AND TOXICITY

Side reactions from antihistaminic drugs are rather frequent. Sedation, differing mainly in degree, is one manifestation that is common to practically all of these and other related drugs not discussed here. Of the drugs discussed in this paper benadryl produces the most marked sedation, antistine the least while the other drugs are intermediate in this action. The sleepiness from benadryl may be so intense that the patient may be unable to be on his feet. Other undesirable actions noted with these drugs are dizziness, lassitude and dryness of the mouth and nose. Additional effects noted at times have been palpitation, headache, gastrointestinal irritation, dysuria, constipation and tightness in the chest.

More serious untoward reactions have also been noted particularly with benadryl. The hypnotic effect of benadryl may promote accidents.[50] Disorientation,[51] marked excitation, epileptiform movements and irrational mind[52] have been reported. Other toxic effects noted have been neuritic

pains[53] and reactions ending in circulatory collapse[54] and unconsciousness. A case of granulocytopenia probably due to pyribenzamine has been described.[55] Two cases of generalized eruptions following the use of pyribenzamine for atopic eczema have been reported.[56]

It is apparent that many of the side actions may be highly undesirable. One or two of the newer drugs, not discussed in this presentation, may be found to be freer from such unpleasant actions. It is important to keep in mind, however, that the possible remote toxic effects from these drugs are still not fully ascertained and may perhaps constitute the greatest hazard. Prolonged observation of blood counts, liver function and other tests will be required to answer this question for every new drug.

SUMMARY

1. The chemical structure of several antihistaminic drugs—benadryl, pyribenzamine, neoantergan, antistine and thenylene—is described.

2. These drugs inhibit histamine shock, prevent bronchospasm following exposure to histamine aerosols in guinea pigs, inhibit the histamine contraction of the guinea pig intestinal strip, prevent the depressor effect of histamine on blood pressure, protect against anaphylactic shock and against contraction of the sensitized intestinal or uterine strip and inhibit the whealing action of histamine, specific antigens and other whealing substances. They also possess a local anesthetic action, act as cerebral excitants in large doses and some of them have an atropine-like action.

3. Clinically, these drugs offer symptomatic benefit to patients with allergic rhinitis, urticaria and angioneurotic edema, serum sickness, atopic dermatitis and many forms of pruritus. They are not very effective in asthma or migraine.

4. The unpleasant reactions are frequent with most of these drugs, benadryl displaying the highest incidence and the most marked effects. Sedation is the outstanding side action. Other unpleasant actions of the drugs are dizziness, dryness of the mouth and nose, weakness, headache, insomnia and gastrointestinal disturbances.

5. More serious toxic actions have been noted. It is important that the possibility of remote toxic effects be constantly kept in mind.

6. It is emphasized that these drugs are not completely effective, that at best they are only palliative and that they do not relieve all phases of allergy. They are not substitutes for other antiallergic remedies such as epinephrine, ephedrine, aminophylline and iodides. While the antihistaminic drugs are valuable additions to our therapeutic armamentarium, they do not obviate the need for the more basic and lasting effects of specific allergic management by methods of avoidance and desensitization.

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Allergic Dermatitis*

A View of Its Immunologic and Biochemical Implications

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ALLERGIC dermatitis includes those inflammatory lesions believed to result from an altered state of tissue reactivity which renders the skin unusually sensitive to substances that ordinarily do not evoke grossly demonstrable reactions. The dermatitis may be acute. More often it is chronic with recurring exacerbations. The lesions are erythematous, vesicular or papular. In the more acute and active stage, when the epidermis is edematous, the lesion is frankly exudative or eczematous. Itching is the common symptom. It is often severe and leads to traumatization by scratching. Trauma is frequently a major factor in prolonging the dermatitis as may also be secondary pyogenic infection or mild irritation from numerous sources.

In the acute stage of dermatitis the skin has a mildly swollen appearance and histologically there is edema both of the vascular corium and the avascular epidermis. In the epidermis the presence of fluid gives a varying picture which depends upon the degree of edema. When minimal, there may be only vacuolization of the epithelial cells. When in excess, there is palpable vesiculation and in extreme cases bullous formation.

In the chronic stages of dermatitis the skin becomes dry and thickened, and the surface markings are exaggerated. This gives the skin a lichenified appearance. In both the acute and chronic phases there is disturbance of epithelial keratinization which gives rise to desquamation of the keratinized or partially keratinized cells. In extreme cases, as in arsenical dermatitis, there is often widespread exfoliation and the tissues are edematous and highly inflamed.

The terms used to describe the dermatitis are many. Eczema is perhaps the most common. When the lesion is chronic and the skin lichenified, it is at times called neurodermatitis. In addition there are terms which attempt to suggest the cause or some underlying mechanism. Among these are atopic dermatitis, contact dermatitis, or dermatitis venenata, and drug dermatitis, or dermatitis medicamentosa. These and still others would seem to fall within the scope of allergic dermatitis.

The allergic dermatoses have been placed in two categories depending upon the source of the excitant, and the route of contact, namely, intrinsic and extrinsic allergic dermatitis. In the intrinsic type the sensitizing agent enters the body chiefly through the gastrointestinal tract or by the vascular system as in the intravenous administration of therapeutic agents. In the extrinsic type contact is directly with the cutaneous surface.

This differentiation is of advantage only from a clinical point of view since it is doubtful whether the route of exposure carries any essential immunologic significance. It is generally assumed that the dermatitis in either case is related to an antigen-cellular antibody reaction. Although this explanation is based chiefly upon hypothetical grounds, the associated clinical circumstances and immunologic phenomena seem sufficient justification for the assumption. The theory will serve at least for the present even though it is probable that new knowledge will in time prove it inadequate as a definitive explanation.

It may be helpful to an understanding of

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the presently conceived relation of the integumentary system to the allergic state to consider briefly the historical developments which have brought these inflammatory lesions into the area of allergy. As early as 1895, Jadassohn showed that patients with eczematous dermatitis, attributed to extrinsic causes, reacted with a similar dermatitis when small amounts of the suspected exciting substance were applied directly to uninvolved areas. However, it was from a different direction that observations were to demonstrate more clearly the relationship. This was the introduction of horse serum to the treatment of diphtheria, with its attending serum sickness and associated cutaneous lesions, and the identification of this reaction with anaphylaxis. Even though the anaphylactic animal did not respond with cutaneous lesions characteristic of serum sickness in man, it was obvious that the urticarial wheal and its associated vascular phenomena were functions of sensitization to a foreign protein. The similarity of the cutaneous sensitivity demonstrated by Jadassohn in eczematous dermatitis to that accompanying serum sickness became apparent when it was shown that the skin of a person sensitized to horse serum reacted locally to the foreign protein and that skin sensitizing substances were demonstrable in the blood.

Postulates of Allergy. In testing for sensitivity two kinds of cutaneous response are observed in man: One is an immediate and transient reaction in the form of erythema and an urticarial wheal. This follows at the site of intradermal contact with the antigen. The other is a delayed response coming within twenty-four to forty-eight hours after direct contact of the unbroken skin with the antigen. This reaction is inflammatory and often vesicular.

In the immediate reaction the tissue changes are those of edema and hyperemia. They are temporary and reversible and are related to vasomotor disturbances and imperfections in permeability of the vascular membranes. Its clinical counterpart is urticaria and the functional erythemas, also angioneurotic edema with its more profound disturbance in local fluid balance. In the respiratory tract there is a resemblance to the lesions of the mucous membranes in hay fever.

The delayed reaction affects both the corium and epidermis. The tissue changes, when well developed, are organic and hence not reversible except through the processes of repair. However, the restorative process can now be greatly accelerated in certain cases by special measures. At its maxium, necrosis of the skin may occur, as exemplified by the Arthus phenomenon. The delayed reaction has its clinical counterpart in exudative or eczematous dermatitis. It is analogous to the tuberculin type of reaction.

Although there is no specific histologic pattern which differentiates the allergic reaction, the frequent eosinophilic response may suggest the presence of allergy. Eosinophilia occurs with greater regularity and more prominently in the wheal-reacting form of allergy.

In the blood of the guinea pig and of man sensitized to horse serum are found specific antibodies. These are of three kinds, namely, precipitins, smooth muscle sensitizing substances and others capable of sensitizing the skin. It is around these functions of the sensitized organism, especially the skin-sensitizing antibody, that much of the argument as to the identification of a dermatitis as allergic has centered.

The differentiation of allergic disease in man depends upon the isolation of the offending allergen and the demonstration of its ability to excite the particular tissue or tissues to activity or upon amelioration of the reaction by removal from contact with the excited tissues. Secondly, it depends upon the demonstration of skin sensitivity to the specific antigen or of skin-sensitizing antibodies specific to the antigen, preferably both.

Although immunologic evidence of allergy may be demonstrated with some regularity in anaphylaxis and serum sickness, it is not so readily demonstrable in all the so-called allergic diseases of man. It is the

failure to satisfy the postulates of allergy and the inability, where these criteria are present, to relate them specifically to the clinical disease which has led to confusion. Often the results of such studies are equivocal and there is no way of establishing the relationship of the disease to the allergic state or of demonstrating what contribution the state of allergy may make to the pathogenesis of the lesion. It is with these uncertainties that we are faced in the study of allergic dermatitis.

Intrinsic and Extrinsic Sensitization. As we have already stated, allergic dermatitis may result from either intrinsic or extrinsic contact with the causative agent. While in some instances the form of lesion and the distribution of the eruption suggest the mode of contact, at other times this differentiation is quite impossible. When the contact is intrinsic one would expect to find the seat of reaction in the corium. There would be the usual signs of inflammation. The nature and form of the lesion would depend upon the grade of inflammation and the extent of edema and extravascular cellular infiltration. In the acute and milder grades of inflammation vascular dilatation and edema not differing much from the urticarial reaction would be present. No hard and fast line can be drawn at times between the urticarial and dermatitic response. One may occasionally observe an urticarial reaction, or something closely approaching it, preceding the inflammatory reaction. This is often true of arsenical dermatitis. The condition known as erythema multiforme is a classical example of a reaction that at one and the same time shows the signs of urticaria and dermatitis. It evolves with the suddenness of urticaria and lingers with the persistence of a dermatitis. Occasionally, it may show small hemorrhages into the skin or, perhaps, bullous edema. There may be lesions of the mucous and synovial membranes and involvement of the viscera. Osler once likened the condition to anaphylaxis. When the inflammatory process is more chronic, papulation of the skin may be found and a state of lichenification may be present.

In the extrinsic form of dermatitis the epidermis is the primary seat of sensitization. As the epidermis is avascular and composed wholly of epithelial cells, inflammation necessarily takes a different form than in the highly vascular corium. The lesion consists of accumulated fluid and a vesicle or bulla is formed. Vesiculation is the mark of epidermal reaction and exudation that of vesicular rupture.

Actually, however, whether the injury comes from within or without, both the corium and the epidermis show signs of disease. It is only the preponderance of reaction in one or the other part of the skin which may suggest the primary seat of sensitization. The complex reaction comes from the rapid diffusion of the irritant from the corium into the epidermis, or vice versa.

Histamine. It has long been the impression that anaphylactic shock in the experimental animal and the allergic reaction in man may be related to a basic causative mechanism. It was early observed that the symptoms of anaphylactic shock were strikingly similar to those of histamine shock. Both Shultz and Dale were able to demonstrate that the isolated and perfused uterus of the sensitized guinea pig contracted forcefully upon contact with the sensitizing antigen in a manner identical with histamine. It was some twelve years later before the urticarial wheal was to be related to the same mechanism.

Lewis and Grant,[1] while studying the physiology of the blood vessels of the human skin, had their attention directed to the urticarial lesion which resulted from mechanical injury to the skin of certain susceptible persons said to be dermographic. This urticarial response to a single firm stroke on the skin they believed was set in motion by a diffusible substance similar to histamine which was released in the skin by the stroke. Susceptible subjects differed from normal subjects only in their susceptibility to injury. All persons reacted in a similar manner when the grade of injury was suffi-

cient. Agents evoking the reaction had one property in common, namely, they produced damage to the tissues. By this action it was believed a substance is released which sets in motion a triple reaction consisting of a red line, a surrounding flush and a wheal. The first and last of the three components of this reaction are local in origin; the flush surrounding the wheal was shown to depend upon a nerve reflex. The triple response they considered a physiologic expression of a general mechanism of defense in the skin against injuries of all kinds. In the susceptible person it attracts attention only because of the relatively mild grade of injury required to liberate the diffusible substance.

Histamine is a normal metabolite which, according to Code,[2] is not the fundamental factor in anaphylaxis or in allergic reactions. It is liberated only as a consequence of damage done to the sensitized cells. It is the damage that is essential to the allergic or anaphylactic reaction; the liberation of histamine is purely incidental. Heparin is also liberated in some species and affects the coagulability of the blood.

In recent years it has been suggested that acetylcholine,[3] a mediator of parasympathetic nerve impulses,[4] is the chemical mediator of anaphylaxis or of the allergic reaction. There has been some speculation as to whether this effect might be due to an excess of acetylcholine or to inhibition of its catalysis through some defect of the choline esterases. Others were unable to demonstrate the presence of acetycholine in excised tissues from allergic animals.[5]

Although it is possible that histamine may be released in allergic disease, there seems to be no direct evidence that such is the case. Fluctuations in the histamine content of the blood in patients with allergic diseases such as asthma, hay fever and dermatitis are greater than in normal man but are not necessarily correlated with the onset of symptoms. Rose[6] could detect no variation in the histamine content of the blood in recurrent urticaria although others have noted an increase. In angioneurotic edema the level of histamine in the blood showed a moderate to marked decrease while symptoms were at their height and returned to normal limits after their subsidence.

The action of the antihistamine substances, benadryl and pyribenzamine, on the manifestations of allergic disease in man have not clarified the position of histamine in the allergic reaction.[7] Except in urticaria, these drugs have not controlled the reaction to a significant degree. Even in urticaria the results are variable and withdrawal of the drug is followed by the recurrence of lesions. There is little or no evidence that either benadryl or pyribenzamine affect allergic dermatitis except in allaying the itching. Nor would such an effect be expected in view of the assumed relation of histamine to the allergic reaction.

Allergy and Dermatitis. The basis for the assumption that allergy is a force in the causation of dermatitis and that the mechanism is related to an antigen-cellular antibody reaction rests upon two prime observations: The first is its frequent occurrence in persons with an immediate urticarial type of cutaneous reaction to antigens derived from certain foods and inhalants. Such persons frequently also have or later come to develop allergic diseases such as hay fever and asthma. Among those individuals there is apt to be a familial history of allergic disease. The second factor is a manifest sensitivity to foreign substances in small quantity, substances which ordinarily are not productive of dermatitis and which cause entirely different effects in the allergic state than they do in the non-allergic state.

Related to the first is the dermatosis which by some is called atopic dermatitis, a term of doubtful propriety which includes the eczematous eruptions of infancy and childhood as well as similar dermatoses incident to adult life. All these, in the minds of most, are eczema.

The second includes the drug eruptions in which the immunologic and familial evidence of allergy found in the so-called atopic group is generally absent. Evidence of specific sensitization can often be adduced

in the drug sensitivities. There may be a tangible history of first exposure and the subsequent effect of the drug is often immediately apparent even to the patient. The second also identifies an extrinsic dermatitis due to contact with certain plants and chemicals. As in the drug sensitivities of intrinsic origin, immunologic and historic evidence of the allergic constitution is usually lacking. Unlike the drug allergies, however, there is greater difficulty in identifying the causative agent. Poison ivy and primula dermatitis are perhaps the best known examples of extrinsic allergic dermatitis.

The immediate urticarial skin reaction cannot be demonstrated in the chemical sensitivities whether they proceed from intrinsic or extrinsic contact. It seems possible, however, that this failure may be due to the use of the wrong allergen in that the simple chemical rather than its protein conjugate is used in the testing. In such cases, when specific cutaneous sensitivity can be demonstrated, it is a delayed inflammatory type of reaction not an urticarial reaction. There is good reason to suspect that the state of sensitivity existing in either case does not suffice to explain fully what goes on to produce the dermatitis.

Intrinsic Allergic Dermatitis. We will discuss two varieties of intrinsic allergic dermatitis: one occurs in infancy and childhood, the other in persons who become sensitized to arsenical drugs. The first is commonly known as infantile eczema or atopic dermatitis, names which we would prefer to replace with the simple term, exudative dermatitis. This name is fairly descriptive anatomically and, since the cause of the dermatitis remains obscure, carries no etiologic connotation. In older persons a similar dermatosis goes by various names, including neurodermatitis. We have chosen arsenical dermatitis as an example of the second variety of intrinsic allergic dermatitis because of our familiarity with it and also because recently acquired knowledge concerning it opens to view a mechanism which may have a significant bearing on dermatitis from other causes. Although the dermatitis of infancy differs in many respects, historically, clinically and immunologically, from arsenical dermatitis, a fundamental similarity in their genesis seems not improbable.

Exudative Dermatitis of Infancy. The skin of the infant, whatever the nature of the injury, tends to react with a more edematous lesion than does the skin of the adult. The lesion is apt to be vesicular or bullous. Causes as diverse as the bite of an insect or infection with pyogenic cocci or Treponema pallidum frequently cause vesiculation or bullous formation in the infant. The epidermis, the seat of all such lesions, seems especially vulnerable to injury and reacts acutely in the only way given it, that is to say, by the accumulation of fluid. In the adult a well developed edematous component is less often observed, especially in the conditions mentioned above. The inflammatory reaction is often greater in the vascular corium where it is marked by a preponderance of extravascular cellular activity and edema. Such differences are perhaps only quantitative; nevertheless they indicate less stability of the epidermal tissues in infancy than in adult life. At least, allergic dermatitis in infancy is usually exudative and the skin has a plethoric appearance. In the adult the dermatitis is inclined to be hyperplastic and dry. Between the two extremes lie many variations.

Certain epidemiologic aspects of eczematous dermatitis in infancy have been repeatedly emphasized as significant indications of the allergic nature of the dermatitis. It is stated that as many as 50 per cent of infants with dermatitis give a familial history of allergic disease among their antecedents. A like history is obtainable from children who have asthma and hay fever. We were not, however, able to find any record of the frequency with which infants, unaffected by dermatitis or other allergic diseases, have a similar familial history. The statement is made that they do not; nevertheless it seems desirable for the sake of accuracy that this point be established beyond doubt. One criticism of similar con-

clusions drawn from the study of allergic disease is that they are often based on percentages dealing with highly selected samples, sometimes inadequate in number to give the noted differences statistical significance; or if the differences are of that magnitude, the bias introduced by the method of sampling is such as to invalidate the conclusions.

It is also asserted that 50 per cent of children who manifest eczematous dermatitis already have asthma or hay fever or will develop these diseases before they reach the age of ten years. This would appear to be a highly significant correlation. However, one would want to ask about those infants with dermatitis who do not grow up to have asthma, and hence are not taken into account; for it is assumed that only those who develop asthma later in life consult a physician and thus get into the clinical sample. In other words, the conclusion is based on a sample of asthmatic children and not upon the entire population of once eczematous infants.

Regardless of any fallacy which may be involved, we will assume for the purpose of the argument that ample reason exists for including the dermatitic and asthmatic children in the same group, thus relating dermatitis to allergy. Besides there are other functions which would relate the eczematous reaction to the allergic state. These have provided abundant reason for differences in opinion as to the significance of allergy in the causation of dermatitis.

Infants affected with dermatitis frequently carry skin-sensitizing antibodies in their blood and, when tested with antigens prepared from foods or inhalants, develop immediate wheal reactions at the site of contact. Multiple sensitivities occur in half of those tested. Among 100 such infants whom Hill[8] tested, local wheal reactions to egg albumin appeared in eighty-seven infants, twenty-six reacted to milk and seventeen to wheat. It was his belief that "sensitivity to the protein of cow's milk is probably the most important single cause of atopic dermatitis in infancy." Concerning egg white, to which most of the infants reacted, he concluded that it could be of little importance as a causative factor in the dermatitis since most of the infants had never eaten eggs; and when it was removed from the diet of those who had eaten it, there was usually no effect on the dermatitis. So far as egg was concerned, it seemed necessary to differentiate the allergic state from allergic disease. But what of milk? By the same token was there any more reason to implicate it than the egg? Apparently not, for the same author went on to say, "I have seen nothing in the literature, including my own contributions, which leads me to believe that anyone really understands infantile eczema or that there is now any method of treatment, dietetic or otherwise, that is consistently and entirely satisfactory." It seems altogether probable that too much significance has been attached to the immediate wheal of the skin test in the eczematous child and, for that matter, in the eczematous adult.

It remains obscure why the infant who at birth shows no sensitivity to egg white later develops this sensitivity without having eaten eggs. The phenomenon seems to occur in those infants predisposed genetically to the allergic state and later to allergic disease. Those who do not possess this apparently heritable capacity do not develop skin-sensitizing antibodies, even when fed egg white in quantity, nor do they develop dermatitis, asthma or hay fever.

It has been demonstrated that 30 per cent of millers and bakers who are exposed to cereal dusts have wheal reactions to skin tests with cereal antigens but normally manifest no disease from this exposure.[9] At the other extreme is the person who, receiving an injection of horse serum for the first time, dies in anaphylactic shock. And as yet no one, by artificial sensitization of man, has succeeded in producing any of the diseases attributed to allergy which spontaneously develop at different ages.

In eliminating the wheal-reacting type of allergy as of immediate significance in the production of allergic dermatitis, there are

the revealing observations of Hampton, Wing, Boker and Cooke[10] who tested approximately sixty infants and children, all with typical eczematous dermatitis. This they did by passive transfer of skin sensitivity through the use of blood serum. Half of those tested gave positive wheal reactions to foods and inhalants. The others gave no reaction. The nature and course of the dermatitis were the same in both groups. The familial incidence of allergic disease was also equally divided. Asthma was present in ten patients.

In a second group of twenty-seven patients, who were hospitalized for dietetic study, fifteen had asthma, urticaria or hay fever in addition to dermatitis. When tested by passive transfer, the serum of seventeen children gave typical immediate wheals to one or several foods. In thirteen instances these tests were verified by a direct skin test. In an attempt to prove or disprove the causal relationship of the allergen giving a positive skin reaction to the dermatitis, it was found that the foods concerned could be eaten abundantly and continuously without any exudative skin reaction. In patients acutely sensitive to egg, peanut or honey, feeding of these foods caused urticaria to appear promptly but never dermatitis. The children could eat all other foods in quantity and indefinitely without developing any exacerbation of the dermatitis. It was thought that inhalant antigens such as pollens, danders and dusts could be excluded readily as causes of the dermatitis.

These observations afford the most critical test yet to be reported which would nullify the factor of specific sensitivity to foods and inhalants as the principal cause of allergic dermatitis in infancy and childhood. The presence of skin-sensitizing antibodies of the immediate wheal reaction type does not specify the dermatitis as being directly related to the allergen or allergens responsible for the positive results of the skin tests. Nonetheless, the frequent association of the allergic state with the dermatitis would indicate that enhanced tissue sensitivity contributes in some way to the readiness with which cutaneous tissues respond to an injury not yet identifiable.

Thus far the central interest in the problem of allergic dermatitis has been directed toward the immunologic aspects of the disease and the technics of investigation have consequently been limited to those of the immunologist. But the results have been indifferent; a fresh point of view is badly needed. It is somewhat surprising, therefore, that until recently so little attention has been given to the observations of Hansen and his co-workers[11] who, in 1933, published the first of a continuing series of papers dealing with the essential fatty acids and the eczematous patient. It is not unlikely that from this or similar advances in the problem will come knowledge which in time may identify important metabolic faults as essential factors in the causation of eczematous dermatitis of this type.

Seborrheic Dermatitis. Seborrheic manifestations often precede an exudative dermatitis in the infant,[8] especially in fat babies in the early months of life. The process may begin with intertriginous inflammation in the large folds of the skin or as greasy scaliness of the scalp, the so-called cradle cap. From thence the eruption may extend to the face, neck and to the trunk. The lesion is a dry scaliness with only faint signs of inflammation. There is no exudation. The scales may be so dry and profuse at times as to suggest psoriasis; more often they are yellowish and greasy. Unlike eczematous dermatitis, itching is not a symptom nor does the skin react to the tests for protein sensitivity. There is no evidence of an allergic state. After a few weeks or months, permanent recovery may ensue or the skin may become eczematous and exudative dermatitis may develop with demonstrable allergic sensitivity.

The sequence of seborrheic and exudative dermatitis occurs often enough to suggest a causal relationship. The fact, that in the one there is, as a rule, no evidence of allergic sensitivity and in the other such evidence is so often adduceable, leads one to suspect

that the development of cutaneous sensitivity may be a factor in the metamorphosis.*

Drug Dermatitis. Idiosyncrasy to certain drugs and chemicals is manifest in a variety of cutaneous disorders in man, usually after the first contact or at times after prolonged contact with a substance that had been well tolerated. Only small doses of the drug are required subsequently to evoke the cutaneous response often reproducible over a long period of time. The similarity to protein sensitization led von Pirquet to include the drug idiosyncrasies among the allergic diseases. Investigations were later carried out on the sensitization of animals to simple compounds of a non-protein nature known to cause hypersensitiveness in man. Arsphenamine was found to produce "symptoms like those seen in anaphylaxis" in guinea pigs which were sensitized with a mixture of the drug and homologous serum and then injected with the same mixture after a suitable period of incubation.[12] Others observed cutaneous reactions in guinea pigs sensitized to arsphenamine but found the reaction variable with the diet, namely, green fodder inhibited and dry fodder favored the sensitization.[13] Cutaneous sensitivity through extrinsic contact was induced by *p*-phenylenediamine but with greater ease, perhaps because of its firm chemical union with proteins of the skin after oxidation.[14] And more recently, anaphylactic shock has been produced with simple chemical compounds, for example, in animals sensitized to azoproteins and injected with azodyes having the same azo component.[15] The reaction was specific and occurred with quantities of the dye as small as a fraction of a milligram.

Most authors thought the simplest explanation of the mechanism of hypersensitiveness to simple chemical compounds was to relate them to the familiar processes of immunization, especially in view of the specificity of the reactions, and to assume a combination of the compounds with protein (as was probable in the case of *p*-phenylenediamine). Rabbits had also been sensitized to formaldehyde by immunizing them with formalinized protein.[16] Then Landsteiner got the same effects by using arsphenamine alone.[17]

Perhaps the chief difficulty in explaining the phenomenon of hypersensitiveness to the chemical substances lay in the uncertainty of demonstrating circulating antibodies even in the pronounced cases of human drug sensitivity. How important an objection this may be remains a question. Nevertheless, it is not necessarily true that when no antibodies are demonstrable in the blood they may not be on the sensitized cells. However this may be, there are reports of the occasional demonstration of such antibodies in cases of human idiosyncrasy to iodoform, iodine, mercury and to other similar substances. Recently, sulfadiazine has been added to the simple chemical compounds shown to stimulate the formation of demonstrable antibodies in man and to react with these antibodies in the passively sensitized skin.[18] From such evidence there would seem to be ample reason for including the drug eruptions among the allergic dermatoses.

The variety of anatomic lesions caused by drugs is limited only by the skin's capacity of reaction. No one form of lesion is identified with any one drug although certain drugs tend to produce lesions of similar character. Arsphenamine, for example, causes reactions which vary from a simple urticaria to exfoliative dermatitis, with the intermediate lesions of multiform erythema and purpura. Not infrequently all may be observed in the same person as they develop in sequence from urticaria to diffuse erythematous dermatitis with edema, exudation and, finally, exfoliation. At times the reaction is transient, as in urticaria; or again it may persist for weeks and even months as a severe inflammatory and ex-

* In North China, exudative dermatitis of infancy is an infrequent disease among the mass of common people as is also seborrheic dermatitis. This fact may carry some significance in view of the dietary habits of these people[41] and the observed high unsaturation of their serum fatty acids.[42] Dietary fat is derived almost entirely from vegetable oils, the bulk of which consists of unsaturated fatty acids.

foliative process. Other drugs such as the sulfonamides may cause bullous formations which merge into chronic exfoliative dermatitis; or again hemorrhage may be the only sign of sensitization in the form of purpura when the skin is involved or of diffuse bleeding in other organs such as the brain. Nodose erythema occurs at times with the bromides and nodose periarteritis with the sulfonamides.[19,20]

In their action as antigens, drugs not only vary in the form of lesion produced and in the organ affected but also, like living pathogenic organisms, they vary in the ease and frequency with which they cause disease in different species and individuals.

While many of the cutaneous lesions occurring in drug sensitization are erythematous and urticarial in type and perhaps caused by the release of a histamine-like depressor substance, most are of the delayed reaction type in the form of a dermatitis which is indicative of a more profound and lasting derangement of cellular metabolism. The inflammatory lesions are not immediately reversible as are the urticarial lesions. During the period of acute urticarial response, adrenalin often effects prompt resolution of the lesion as in serum sickness and at times in the urticarias of drug sensitization. The antihistamine drugs, benadryl and pyribenzamine, act likewise but when the reaction has gone beyond the early stage of whealing and hyperemia, as in the multiform erythematous lesions and dermatitis of arsphenamine sensitivity, they are ineffective except as they may allay the itching. Inasmuch as the dermatitis in such cases continues to be progressive beyond the period of effectiveness of the antihistamine drugs, it is only reasonable to assume that factors other than histamine must be sought to explain the dermatitis. When once the process has become inflammatory, the urticarial phase of the reaction vanishes not again to appear. If histamine is a force in the production of the cutaneous lesion, it must act early and not after cellular degeneration has commenced. It seems not unlikely that once the junction of antigen and antibody has taken place, presumably with the release of a histamine-like substance, the process is carried forward by other mechanisms quite distinct from the antigen-cellular antibody reaction.

Extrinsic Allergic Dermatitis. The extrinsic type of allergic dermatitis differs from the intrinsic variety primarily in the route of contact with the sensitizing agent. The site of sensitization is initially in the epidermis, the outermost layer of which is composed of a protein, keratin, together with an admixture of fats. Hence it is the epidermis which develops the preponderant reaction, with extreme grades of vesiculation like that seen in poison ivy dermatitis. Almost at once, however, hyperemia also appears. Although this phase of the reaction is often moderate as compared with that in the epidermis, it indicates the rapid diffusion of the excitant, or a derivative, into the denser and more vascular structures of the corium. Unlike some cases of intrinsic dermatitis due to chemical substances the initial urticarial phase of reaction is absent. From the first the lesion appears inflammatory.

In the drug eruptions as well as in eczematous dermatitis of infancy the initial reaction is in the corium but this is almost always followed either by mild edematous or vesicular changes of varying grades in the epidermis. The skin reacts as a whole. For this and other reasons, even though it is convenient to consider allergic dermatitis as either extrinsic or intrinsic, little is to be gained from holding to this convention longer than to establish the facts of contact. The reaction in either case is apparently actuated by the same or closely related mechanisms and these would appear to be closely related to that of anaphylaxis. This would seem to be true at least of the dermatoses following chemical sensitization. In the case of eczematous dermatitis of childhood and its counterpart in the adult, the parallelism is more obscure. Nonetheless, in thinking of the allergic dermatoses it seems reasonable and desirable to hold them as intimately related to a common factor, namely, a state of altered tissue reactivity

in which the threshold of tissue resistance is lowered.

Increased irritability is acquired by previous contact with the allergen. This is shown in the case of sensitivity to poison ivy by observations on the infant soon after birth[21] and on the Eskimo[22] who has always resided beyond the zone of exposure. In both, the absence of cutaneous sensitivity to contact with extractives of the poison ivy plant, Rhus toxicodendron, has been demonstrated. However, a few weeks later, 75 per cent of the infants who at birth were found non-reactive responded with a dermatitis at the area of second contact, showing that they had been sensitized by the first exposure. It is estimated that a similar incidence of reactivity exists in the adult population of the United States. In England primula or primrose dermatitis is prevalent. As in the case of poison ivy, after the application of the leaf of Primula obconica for several days to the skin of a normal person, without any sign of reaction, an acute dermatitis was found to appear on the second day after the leaf was again applied if an interval of several weeks had elapsed between the two applications.[23]

The frequency of sensitivity to poison ivy in America corresponds to that for horse serum in those previously exposed by treatment. Other environmental substances which at times provoke dermatitis do not show this widespread distribution of sensitization in the population. Schwartz and Tulipan[24] state that in twelve industries, where continuous contact with known sensitizing chemicals exists, the annual incidence of allergic dermatitis is around 1 per cent. A similar incidence of sulfonamide sensitization is suspected. It is of interest, too, that about the same percentage of infants is estimated to develop eczematous dermatitis.

Sensitization with Simple Chemical Compounds. The mechanism by which simple chemical substances sensitize tissues has been the cause of much study. The fact that *p*-phenylenediamine (ursol), a sensitizing agent commonly employed in the dyeing of fur and hair, upon oxidation combines readily and firmly with proteins, led to the assumption that the chemical is active antigenically because of a protein conjugate formed in the tissues. Strong evidence of this was found in a study of chloro- and nitro-substituted benzenes. One of these substances, 1,2,4-chlorodinitrobenzene, is a frequent cause of allergic dermatitis in factories where it is handled. As there are theoretically more than 90 chloro-and nitro-substitution products of benzene, it was possible to study the correlation between sensitizing capacity and any chemical characteristic. It turned out that those products which do not sensitize the skin were resistant to treatment with an organic base (aniline) and with one exception to treatment with sodium methylate and ethylate. Those that were potent sensitizers contained loosely bound Cl or NO_2 and formed substitution compounds with aniline by interacting with the amino group. From these observations Landsteiner[25] concluded that the sensitizing chemical, 1,2,4-chlorodinitrobenzene, and compounds having similar chemical activity depended upon conjugation in the body, probably with proteins. These findings were corroborated on human beings.[26]

This led to a study of similar compounds such as acyl and benzoyl chlorides and acid anhydrides. These, too, were found to sensitize animals, presumably through their union with proteins in the body. Most informative, however, was the relationship between reactions of the skin and anaphylaxis caused by acyl chlorides. Guinea pigs were sensitized with *p*-chlorobenzoyl chloride injected intracutaneously. After a suitable interval, the skin was found to react with a dermatitis after direct application of the substance, and when a compound of *p*-chlorobenzoyl chloride and guinea pig serum was injected intravenously the animals developed typical anaphylactic shock. From these observations it was inferred that the two types of allergic manifestation are closely related.[27,27a]

In the case of extrinsic dermatitis in man, sensitivity can be demonstrated only by sur-

face contact with the allergen. The reaction is delayed and in the form of a dermatitis. Skin-sensitizing antibodies of the immediate wheal reaction cannot be demonstrated in the blood nor can sensitivity of the delayed reaction type be produced by passive transfer to normal subjects.

The production of cutaneous sensitivity of the delayed reaction type is far more easily achieved experimentally by direct application of the antigen than by other routes which as a rule are not effective. When sensitization has been established, however, introduction of the allergen through the gastrointestinal tract or through the blood may evoke a dermatitis at the previously sensitized area. This is observed in human cases of mercurial and sulfonamide sensitivity. To our knowledge it does not occur naturally in sensitization to poison ivy in which it would appear that direct contact with the excitant is required to produce a dermatitis. It is also worthy of note that in the extrinsic form of allergy in man the skin plays the most prominent if not the only rôle in the allergic process. Desensitization of the skin has not been achieved. Eosinophilia does not develop as it does in the intrinsic form nor is there any reason to believe that histamine takes any part in the reaction.

The question has arisen in view of these facts whether or not the skin can be sensitized directly without the participation of free antibodies as by the contiguous distribution of the allergen through the skin from epithelial cell to epithelial cell. If circulating antibodies are not present, it is necessary to account for the phenomenon of generalized sensitivity of the skin which exists in many cases. This question seems to have been definitely settled by Landsteiner and Chase[28] who showed that the allergen is transported by way of the lymph vessels lying on the surface of the muscular layer in the skin of the guinea pig. When these vessels were interrupted, sensitization beyond an isolated area of original contact did not take place.

BIOCHEMISTRY OF VESICULATION

Vesiculation or lesser grades of epidermal edema are characteristic of allergic dermatitis. For this reason it seems not unlikely that the biochemical lesion of artificially induced vesiculation may be closely related to that of allergic dermatitis. Some vesicants are known to be antigenic. Others are related chemically to the trivalent arsenical arsphenamine which sensitizes man and causes dermatitis. The same chemical substance, which prevents vesication upon contact with lewisite and other arsenical vesicants or restores the damaged skin, also has a curative action in allergic arsphenamine dermatitis. These facts strongly suggest a common biochemical mechanism. Even should this prove to be an unwarranted assumption, the facts as they exist are so intriguing that a discussion of their possible implication is desirable.

The vesicant action of arsenicals and other similar substances is conditioned by their ability to penetrate the keratin layer of the skin and thus reach the site of blister formation in the epidermis and also of vascular reaction in the small blood vessels of the deeper layers. In some instances, as with arsenious oxide, only prolonged and intimate contact with the skin may produce erythema and vesication. The arsenical vesicant, lewisite, being lipid-soluble, rapidly penetrates the epidermis where it is hydrolyzed immediately to the corresponding toxic oxides.[29]

There is now an impressive body of evidence that the toxic effects of arsenicals are primarily related to the fact that they combine with —SH groups in the tissues and thus inhibit enzyme systems essential to cellular metabolism. When arsenic combines with tissue proteins, reactive —SH groups disappear[30,31] and the closer the union the more serious the effect on the cell. A series of enzyme proteins containing free —SH groups are reversibly inactivated *in vitro* by arsenicals with the disappearance of titratable —SH groups.[32] This implies that

the toxic action of arsenicals is referable to similar sulfhydryl enzymes in living cells.

When lewisite ($ClCH{=}CH{\cdot}AsCl_2$) reacts with keratin, 75 per cent of the bound arsenic is in combination with two thiol groups.[29] This suggested the formation of a relatively stable ring structure. It seemed possible, therefore, that the high toxicity of trivalent arsenicals might be due to their combination with essential —SH groups in certain tissue proteins to form stable arsenical rings. If this assumption were correct, dithiols might combine to form relatively stable ring compounds with lewisite or other trivalent arsenicals and so compete effectively with dithiols of tissue proteins to protect the enzyme systems.[33,34]

It was discovered that all vesicants, which comprise a heterogeneous group of most diverse chemical characteristics, inhibited carbohydrate metabolism of the skin, indicating that carbohydrates could no longer be utilized. There is strong circumstantial evidence that many vesicants act at the stage of initial phosphorylation of glucose by poisoning hexokinase, an essential intracellular —SH enzyme and one which catalyses glycolysis at this point. The pyruvate oxidase system is especially sensitive to poisoning by the arsenicals. In the case of mustard gas, however, it seemed improbable that the poisoning was due to an attack on —SH groups. There was a striking correlation between the vesicating property of any vesicant and its power to alter hexokinase. Reasons were also given for believing that phosphate-transferring enzymes, phosphokinases, belonging to the same group as hexokinase, are inhibited.[29,35]

Some compounds not previously known to be vesicants were found to inhibit the enzyme. Further examination of these showed the apparent lack of vesicancy to be due to rapid evaporation; when held tightly to the skin, vesiculation developed. Non-vesicants always failed to inhibit glycolysis, except that one or two alkyl halides, which produced only edema, gave partial inhibition. The presence of glucose protected the enzyme to some extent and with high concentrations a few vesicants failed to inhibit the enzyme.

The original thesis that the dithiols might act to protect glycolysis was brilliantly established.[33,34] It was proved that the cyclic thioarsenite formed by the interaction of simple dithiols and trivalent arsenicals was more stable than those formed by the interaction of tissue proteins and dithiols. Because of this, the simple dithiols could compete successfully with tissue proteins for such arsenicals as lewisite or phenyldichlorarsine.

This has been amply demonstrated in arsenical dermatitis in man.[36,37] Arsenic bound in the tissues is released as shown by an increased excretion in the urine coincident with the rapid and complete regression of dermatitis.[38] Severe dermatitis from contact with diphenylamine chlorarsine, present as long as eighteen to fifty days, resolved rapidly and completely within two to eight days after the application of the dithiol, 2,3-dimercaptopropanol (BAL or dimercarpol), in ointment to the involved or even to the non-inflamed skin. Arsphenamine dermatitis likewise responded.

In this connection it is worth recalling recent observations regarding the irritating toxicants of poison ivy and related plants of the Anacardiaceae.[39] These are phenols or catechols characterized by a long unsaturated side chain attached to the ring. The reduction of the dermatitis-producing properties of these compounds both *in vitro* and on the human skin may be achieved by the action of mushroom tyrosinase.

The susceptibility of the skin to irritants varies with the species and in the same species among individuals. The skin of the rabbit is resistant to lewisite and reacts only with edema and hyperemia while that of man reacts violently. In both, however, inhibition of glycolysis is demonstrable; the difference is only quantitative.

There is a similar variation among chemical compounds in the power of vesicancy and, here again as in the living organism, variability differs only in the degree of damage to the tissues which they produce.

ALLERGY AND THE BIOCHEMICAL LESION

It is not so much the protective action of the dithiol, dimercaprol (BAL), which interests us as it is the power to restore integrity to the skin in a dermatitis induced by sensitivity to a known chemical compound and the ability to identify the dermatitis with a specific biochemical lesion developing during the allergic state.

Identification of the biochemical lesion is not, however, sufficient to relate the dermatitis directly to the state of sensitivity or to show why it is that the presence of cellular sensitivity predisposes to the biochemical lesion once sensitization has taken place. Perhaps, however, further consideration of arsphenamine sensitization and dermatitis may serve to clarify certain aspects of the relationship.

In arsenical dermatitis a common bond seems to exist between the immunologic and biochemical functions of the allergen. This may or may not be true of other allergens. Instead of the same substance acting both to sensitize the cells and then to poison an enzymatic system, it seems possible that each of these functions might be served by separate entities; one might sensitize, the other might inhibit certain metabolic functions of the cell. The action of the second need not be dynamic as in the case of arsenic; it could be passive as in the deficiency of an essential metabolite. Whatever the variation in detail, the result would be the same.

In any case the cohesiveness of cells and the barrier between the inside of the cell and the outside, the readiness with which the antigen reaches the cell and the ease with which the cell membrane admits molecules of varying dimensions and arrangements must necessarily be critical factors in determining the sensitization and destruction of the cell. It has been suggested that the cell membrane may be a lipo-protein structure,[40] the protein component with active patches rich in —SH groups adsorbed on an underlying lipoid envelope. If such were the case, the permeability of the membrane might be affected by protein molecules denaturized by a hapten with an affinity for sulfhydryl groups. With disturbance in the intercellular fluid matrix and increased permeability of the cellular membrane, changes in water balance would occur and the cell would be exposed to enzyme-inhibiting substances.

The case of arsphenamine dermatitis has several significant features. The immunologic properties of arsphenamine have already been discussed. Even though arsphenamine is immunologically active, it is not a vesicant under ordinary circumstances. Nevertheless, it may behave like a vesicant when applied directly to sensitized skin. This is demonstrated in the occasional patient recovered from an arsenical dermatitis. When a dilute solution of arsphenamine is applied to the intact and non-inflamed skin for a period of twenty-four hours or longer, a mild vesicular dermatitis has been observed to appear at the area of contact. This is the positive patch test. When small doses of the drug are given intravenously under such circumstances, dermatitis does not develop. Nevertheless, the allergic response may be measured by a sudden and transitory rise in eosinophiles in the blood. When doses of therapeutic size are given, a relapse of the dermatitis usually ensues. These facts carry a significant meaning for those cases of dermatitis growing out of sensitization to simple chemical compounds of the heavy metals. They may not, however, fully cover the dermatoses resulting from chemical substances of a different order.

Some of the powerful pupil constrictors, the miotics, such as the alkyl fluorophosphonates and eserine, are enzyme inhibitors.[35] These damage the choline esterases. This fact is of interest because of the probable function of acetylcholine and other vasodilators, such as histamine, in the production of the urticarial phenomena to which Lewis called attention in his study of factitial urticaria. To this we have previously referred. It also offers room for speculation on the neurogenic factor thought to be involved in the urticarias and angioneurotic edema and perhaps in certain cases of

dermatitis in which there may be disturbance in autonomic activity.

Although at present it is not clear how the eczematous dermatitis of childhood and its equivalent in the adult fit into this conception of allergic dermatitis, certain aspects of the eczematous reaction do seem to conform to this line of reasoning. First, the cutaneous reaction is vesicular even though not to the grade seen in poison ivy dermatitis or in some of the intrinsic chemical dermatides. It occurs in persons who are surely allergic, as judged by the presence of skin sensitizing antibodies in the blood, even though the specific sensitivities cannot be related directly to the dermatitis. In persons of eczematous constitution there is evidence of disturbed lipid metabolism as shown by alterations in the fatty acids of the blood. In dogs fed a fat-free diet, changes in the skin occur which in some respects are analogous to eczematous dermatitis or as nearly so as could be expected in a species naturally not responding with a vesicular reaction to any form of irritation. The lesion does, however, resemble quite closely seborrheic dermatitis. These changes can be prevented or the integrity of the damaged skin resorted by the feeding of lard which contains an abundance of unsaturated fatty acids. It seems not unlikely in time it may be found that the eczematous reaction in infancy depends on a deficiency in lipid metabolism superimposed on, or otherwise related to, the allergic state, and like the dermatitis of simple chemical sensitization to be dependent upon interruption of glycolysis or on some inability of sensitized cells to utilize the energy thus provided.

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Drug Allergy*

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THE consideration of allergies due to drugs separate from those due to other agents is, in a sense, an artificial distinction but is warranted by certain practical and theoretical aspects. While most of the common allergic diseases are easily recognized as such and their handling may be relegated to practitioners particularly interested in them, manifestations of drug allergy are commonly encountered in all kinds of medical and surgical practice and must be recognized by specialists in other fields.

Many of the symptoms of drug sensitivity such as fever, leukocytosis, arthralgia, lymphadenopathy, erythema nodosum and scarlatiniform and morbilliform rashes are familiar as manifestations of infectious disease, not of sensitization to naturally encountered extrinsic agents, and their allergic nature might well be questioned if they were not also characteristic of serum sickness which is known to be a protein sensitization. The practical importance of this similarity to infectious processes is attested by reports of fatalities which have resulted when drug fever due to sulfonamides has been confused with a recurrence of infection and the offending drug continued.[1–3]

From the theoretical standpoint, there is reason to hope that further knowledge of drug allergy may contribute not only a broader concept of the manifestations of sensitization phenomena but also a better understanding of the rôle of allergy in the pathogenesis of many of the infectious diseases.

In this discussion, all agents introduced into the body for therapeutic or prophylactic purposes are considered drugs, the reaction to protein drugs such as heterologous antisera forming a convenient link between the familiar protein sensitization and many of the allergies to non-protein crystalloid drugs. Different drugs vary widely in their capacity to produce sensitization, the allergenic activity having no relation to pharmacologic effects. Certain potent drugs such as epinephrine, caffeine and cascara sagrada are not known to cause sensitization while most of the familiar drugs produce such phenomena in occasional persons. A few drugs such as nirvanol and heterologous sera, in adequate doses, sensitize more than 90 per cent of patients.

The term "allergy" in this connection is less susceptible of precise definition. The word was originally introduced by von Pirquet to denote an altered reaction of an individual to repeated contact with an external agent; the presently accepted use of the term is limited to such reactions in which an antigen-antibody mechanism can be demonstrated or reasonably assumed to be present. Most of the naturally encountered allergens are substances not toxic to normal persons and when an individual shows an unusual reaction to one of them its allergic nature is usually manifest. In the case of idiosyncrasies to drugs, most of which in excessive doses are injurious to all individuals, the distinction between allergic and pharmacologic or toxic reactions is often difficult.

There are two criteria upon which the diagnosis of drug allergy may be made with certainty: First, the demonstration of antibodies which is usually possible in reactions to drugs of protein nature but rarely in cases of sensitization to crystalloid substances and second, the occurrence of symptoms typical of allergic disease such

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as asthma, rhinitis, urticaria or contact dermatitis which are entirely distinct from the pharmacologic actions of the drug. A considerable number of other drug reactions, in which an antibody mechanism has not been demonstrated, may be classed as presumably allergic because of the similarity of their symptoms to serum sickness or other known sensitizations particularly by the appearance of symptoms five to fourteen days after the first exposure to the drug which is the time characteristic of antibody formation. On this basis, the drug fever due to sulfanilamide was recognized by Hageman and Blake[4] as a sensitization phenomenon although no antibody was demonstrable.

In recent years, Rich[5,6] and other pathologists have considered certain histologic changes occurring in experimental protein sensitization as characteristic of the allergic reaction and the diagnosis of drug allergy has been made on pathologic grounds in the absence of immunologic evidence. The specificity of these lesions, which will be discussed later in greater detail, has been questioned by Klemperer[7] and they are at present best considered as suggestive rather than diagnostic of allergy.

On the other hand, there are certain drug reactions in which a mechanism entirely unrelated to antigen and antibody is apparent and which can be readily excluded from the classification of drug allergy. Examples are hypersusceptibility to the normal pharmacologic or side actions of the drug and the mechanical results of crystallization of drugs such as sulfadiazine in the kidney tubules.

Between the groups of drug reactions which may be classified as allergic or nonallergic with reasonable certainty, are several important types of idiosyncrasy such as hepatitis, agranulocytosis and thrombocytopenia due to drugs in which the present knowledge of pathogenesis does not permit a definite distinction between sensitization and toxicity. These symptoms are not observed in the common allergic diseases or known protein sensitizations* and an antibody mechanism is not demonstrable. However, these reactions resemble sensitizations in that certain individuals, after prolonged or repeated exposures to ordinary doses of drugs that at first cause no symptoms, suddenly develop an idiosyncrasy and the occurrence of such a reaction predisposes to recurrence on subsequent exposure to the same drug.[8–11] Loewy[12] classified these reactions as "allergotoxic" rather than "allergic" on the ground that certain idiosyncrasies were characteristic of each drug in contrast to the classical concept that sensitization phenomena are the same regardless of the causative agent. This distinction has lost most of its validity with the recognition that not only drugs but all allergens are limited in the sensitization phenomena they produce by the route of contact, solubility, distribution in the body and probably tissue affinity. Because of their clinical importance, these idiosyncrasies will be discussed further in order to elaborate on the evidence bearing on their classification as sensitization phenomena rather than as examples of proven drug allergy.

SYMPTOMS OF DRUG ALLERGY

Asthma and Rhinitis. Numerous drugs, proteins, vegetable gums and crystalloids may act as excitants of asthma and rhinitis on exposure by ingestion, parenteral injection or inhalation (usually occupational). In contrast to most other forms of drug allergy, these manifestations usually occur in persons predisposed by an hereditary tendency to allergy. The attacks precipitated by drugs may be interspersed with those due to other agents and indistinguishable from them. Among the protein drugs causing these symptoms are papain (caroid)[13] and pancreatin. Persons with an

* Although acute thrombocytopenia is a feature of anaphylaxis in monkeys, and certain cases of Henoch's purpura have been shown to be due to food allergy, the reports of thrombocytopenia in man attributed to food allergy are not conclusive.

hereditary allergic tendency have been known to develop asthma on occupational exposure to tuberculin with an immediate urticarial reaction to intracutaneous test rather than the usual type of tuberculin sensitivity.[14] The vegetable gums such as acacia, karaya and tragacanth produce the same type of symptoms. As commercially available and as used for skin tests, these gums contain nitrogen and there is no conclusive evidence whether the allergic reaction is to protein impurities or to the carbohydrate itself.[15] One aspect of practical importance is the widespread pharmaceutical use of these gums as excipients, or cohesive agents, in the manufacture of pills. Brown and Crepea[16] reported the case of a patient in whom the occurrence of asthma and urticaria following the use of pyribenzamine tablets was due to tragacanth used as an excipient and not to the pyribenzamine. Most pills contain some sort of gum, the presence of which is not noted on the label, and the possibility must be considered that reactions following their use may be due to allergy to the gum rather than to the pharmacologically active ingredient. Sensitivity to the gums is readily demonstrable by scratch or intracutaneous tests.

Among the crystalloid drugs producing asthma and rhinitis, aspirin is the most frequent offender but attacks due to quinine, sulfonamides,[17] arsphenamine,[18] penicillin[19] and sulfonechloramides[20] have been reported. Asthma due to soluble and readily diffusible drugs is more immediate and severe than that due to protein antigens and fatal attacks have resulted from doses of 5 to 10 gr. of aspirin.[21,22] It is a familiar clinical observation, as yet unexplained, that aspirin sensitivity is more often associated with the infective type of asthma than that due to foods or inhalants. As will be discussed in considering the immunologic aspects, skin tests with drugs such as aspirin are of no diagnostic value and are exceedingly dangerous.

Urticaria and Angio-edema. Urticaria and angio-edema are commonly caused by drugs (proteins, gums or crystalloids) and in any case of unexplained urticaria all medications the patient is taking must be considered possible factors. Even thiamine, an essential constituent of the body, when injected parenterally in abnormal amounts, may cause a sensitization manifested by urticarial reactions and an immediate positive response to intracutaneous tests.[23–25]

Serum Sickness and Allied Reactions. The symptoms of serum sickness, fever, skin rashes (usually urticarial but often maculopapular or scarlatiniform), edema, lymphadenopathy, arthralgia (sometimes with effusions into the joints) and peripheral neuritis have been reviewed by Longcope,[26] Ratner[27] and others and need be mentioned only because of the frequency of similar manifestations in sensitizations to crystalloid drugs. The incubation period of five to fourteen days after the initial dose is characteristic as is the accelerated or immediate response to subsequent injections in the individual already sensitized.

Reactions indistinguishable from serum sickness, and with the same incubation period, are one of the most common manifestations of sensitization to penicillin of both the amorphous and crystalline forms. Many other drug reactions show one or more of the typical symptoms of serum sickness appearing after the same incubation period.

Anaphylactic Reactions. When heterologous serum is injected into a person already sensitized by a previous injection or with a spontaneous sensitization to this animal protein, the immediate, severe and often fatal reaction characterized by dyspnea, circulatory collapse, urticaria and angioedema resembles experimental anaphylaxis rather than ordinary serum sickness. Similar reactions in varying degrees of severity may occur after repeated parenteral injections of other biologic preparations containing foreign protein or proteose such as insulin,[28–30] liver extract,[31] toxoids[32] and virus and rickettsial vaccines prepared from egg yolk.[33] In the case of persons naturally sensitive to egg yolk, severe reactions may

follow the first injection.* With the doses ordinarily employed, sensitization to these biologicals is much less frequently induced than with foreign sera and the serum sickness type of reaction does not follow the first injection into non-allergic persons.

Anaphylactic reactions (occasionally fatal) may also follow the intravenous injection of crystalloid drugs such as arsphenamine, quinine and thiamine.[24,25] The response to oral administration of drugs is usually slower but a few of the acute, severe reactions to the sulfonamides may be considered in this category.[34,35]†

Drug Fever. One of the most common but most frequently misinterpreted symptoms of drug allergy is fever. Nirvanol, a drug formerly used for the treatment of Sydenham's chorea, produced drug fever in 80 to 90 per cent of the patients who received adequate doses. Similar febrile reactions have been reported to all the common sulfonamide drugs the incidence varying from 2 to 16 per cent with the various drugs. The onset of fever is abrupt, most often on the seventh to tenth day, the incubation period corresponding to that of serum sickness and the usual time of antibody formation. Temperatures of 104 to 106°F. are not unusual, the fever is often but not always accompanied by a skin rash, usually maculopapular. The leukocyte count may remain normal or rise as high as 30,000 with a predominance of neutrophiles, the eosinophiles are only occasionally increased. When the drug is discontinued, the fever usually subsides in forty-eight to seventy-two hours; but subsequent doses after recovery cause an immediate recurrence. Short courses (two to five days) of the sulfonamides may produce sensitization but the drug may be completely eliminated before symptoms develop, so the allergy is first manifested by an immediate reaction to subsequent use of the drug.[36] Among other types of drugs causing drug fever are iodides, thiouracil,[37] atabrine,[38] penicillin[39] and streptomycin.[40] The physiologic mechanism of drug fever is not known nor is its relation to the histologic changes attributed to drug allergy clear. While practically all patients with drug fever recover completely if the causative drug is stopped promptly, it is significant that fever and skin rashes have been outstanding symptoms in many of the cases in which necropsy has revealed extensive vascular and focal lesions.

Drug Rashes. Cutaneous eruptions are the most common manifestations of drug allergy and show many morphologic variations some of which, such as the acniform eruptions due to iodides and bromides, are typical of certain groups of drugs while others are produced by many different agents. The rashes due to the sulfonamides are fairly typical of the common varieties. When the sulfonamides are given by mouth, the indicence of skin rashes is 2 to 5 per cent. The first manifestation is usually a diffuse morbilliform rash appearing, with or without drug fever, on the seventh to fourteenth day of the initial course. If the drug is stopped promptly, the rash usually fades in a few days. If the drug is continued, the rash may progress either to purpura[41,42] or to an intense confluent erythema going on to exfoliation.[43,44] At this stage, the rash fades more slowly after elimination of the drug. The sulfonamides also act as photosensitizers and any of these rashes are made worse by exposure to sunlight.[44–46] Once the skin has been sensitized by the occurrence of a maculopapular rash, subsequent doses of the same drug may produce an intense scarlatiniform rash within twenty-four hours.[41,42,47] The topical application of sulfonamides may also give rise to contact dermatitis, usually a localized vesicular eruption. The controlled studies of Sulzberger and co-workers[48] showed that local applications of sulfonamides over a period of two weeks produced sensitization in 19 per cent of 253 cases, the incidence

* Stull has reported an exceptional case in which injection of equine encephalitis vaccine, made from egg yolk, into a normal person produced a clinical sensitization to egg manifested by gastrointestinal symptoms after eating eggs.

† The mechanism of the severe and sometimes fatal collapse reactions following use of local anesthetics such as pontocaine and procaine has not been clearly established.

being highest if the more soluble compounds, such as sodium sulfadiazine, were applied and also if the application was directed to inflamed or injured skin. Despite the differences in appearance of the eruptions resulting from internal and topical use, the fundamental skin sensitization is apparently similar and once established the reaction may be elicited by either form of contact. Thus, patients who have been sensitized by oral use often show positive patch tests[34] and develop dermatitis promptly on topical application of the drug while those who have recovered from contact dermatitis are apt to have local or general recurrences after oral administration. Although the contact dermatitis usually appears to be a local phenomenon without general reactions, patients with severe cases may develop fever up to 103°F.[49] and patients sensitized by surface contact may react to oral administration of the drug with chills, fever and marked eosinophilia, suggesting constitutional as well as skin sensitization.[48,50,51]

Skin rashes essentially similar to those caused by sulfonamides are produced by numerous other drugs including quinine, mercury compounds, atabrine,[38] arsphenamine, thiouracil,[52] penicillin and streptomycin.[40] In the case of drugs used both topically and internally, the same relationship between the dermatitis resulting from internal use and contact dermatitis is observed.

Contact dermatitis may also be produced by many other drugs used locally such as sulfur, formalin and procaine and other local anesthetics. It does not differ clinically from contact dermatitis due to non-medicinal agents many of which are non-protein in nature.

Space does not permit discussion of all the specialized forms of drug eruptions which have been reviewed by Sulzberger,[53] but two types warrant brief mention. Erythema nodosum is an eruption of characteristic clinical appearance and histologic features of histiocytic proliferation and perivascular infiltration not unlike some of the visceral lesions attributed to sulfonamide sensitization. Lesions with the same clinical and pathologic appearance appear as manifestations of rheumatic fever, tuberculosis and reactions to drugs such as iodides, bromides, sulfonamides,[54] thiouracil[55] and penicillin.[56] When due to drug allergy, they usually appear after relatively long (three or more weeks) exposure to the causative drug, disappear in a few days when it is eliminated but recur promptly on subsequent administration. These lesions are believed to represent sensitization phenomena common to drugs and infections but which have not been known to be caused by other extrinsic allergens.

The fixed drug eruption is of interest as a striking example of localized tissue sensitivity to a systemically absorbed allergen. This type of reaction, caused by such drugs as phenolphthalein, antipyrine, amidopyrine, arsphenamine, alurate[57] and the sulfonamides,[58,59] is characterized by the presence of sharply localized areas of skin or mucosa with an itching erythematous eruption which develops on ingestion of the causative drug. Between exposures the sensitive areas may appear normal or somewhat pigmented. The affected areas of the skin may or may not show positive reactions to patch tests with the exciting agent, the remainder of the skin invariably giving negative reactions. Several experimenters have exchanged skin grafts between the areas involved by fixed eruptions and other areas on the same patient but the results have not been uniform. Naegeli, de Guervain and Stalder[60] reported that a Thiersch graft from an area sensitive to antipyrine remained sensitive in its new site while Wise and Sulzberger[61] and also Loveman[57] found that full-thickness grafts from areas sensitive to phenolphthalein and alurate, respectively, lost their sensitivities in new sites and that normal skin grafted into the affected area became sensitive. From the conflicting results it is not clear whether the sensitivity is inherent in the skin itself or in deeper structures such as the nerves and blood vessels supplying the area.

Hepatitis. Liver damage, which is possibly a sensitization phenomenon, occurs after the use of such drugs as arsphenamine, sulfonamides,[62,63] cinchophen and atabrine.[38] All of these drugs are causative agents of drug fever and dermatitis and frequently the hepatitis is associated with a rash,[11,28,62,64,65] usually exfoliative, which suggests the possibility that both are manifestations of a general sensitization. Hepatitis due to drugs usually appears after exposure over a period of one or more weeks[65] as long as or longer than the characteristic period of antibody formation. The relatively longer incubation periods may be explicable in that tissue changes in the liver are relatively advanced before clinical symptoms are apparent; the occasional appearance of jaundice several weeks after the last dose is difficult to correlate with known antigen-antibody reactions if it is actually due to the drug. When a second course of the same drug is given, hepatitis is more frequent and may appear within one to three days suggesting that sensitization has been acquired.[11,65,66] The occurrence of one attack definitely predisposes to recurrence if the same drug is used again. The incidence and severity of hepatitis bears no relation to the dosage of the drug and the course is uncertain, some cases progressing to liver atrophy even if the causative drug is discontinued promptly.

Agranulocytosis. Leukopenia and agranulocytosis have been attributed to such drugs as amidopyrine, sulfonamides, arsphenamine, thiouracil and gold salts and, as previously noted, show certain features of a sensitization phenomenon. All of these drugs are frequent causes of typical drug allergies. Leukopenia occasionally occurs in patients who have previously manifested sensitization by the occurrence of a drug rash. Agranulocytosis may occur during the second week of continuous administration of amidopyrine[8] while that due to sulfonamides occurs most often between the seventeenth and twenty-fifth days and that those due to thiouracil between the fourth and eighth weeks.[37] Prolonged administration of any of these drugs often causes a mild decrease in the leukocyte count, which may or may not progress to dangerous levels, but in some cases agranulocytosis may occur suddenly. With the use of penicillin to control infection, a majority of patients with agranulocytosis recover within a few days after the causative drug is discontinued. After recovery trial doses of the suspected drug may cause a marked drop of the leukocyte count within a few hours, indicating destruction or elimination of circulating white cells as well as bone marrow damage.[8,67,68] Other patients, in whom agranulocytosis or severe leukopenia have been attributed to sulfonamides[68] or thiouracil,[69] have subsequently been able to tolerate the same drug without reaction.

Thrombocytopenia. Thrombocytopenic purpura due to drugs has many of the features as agranulocytosis and both conditions may occur together as a result of bone marrow depression.[70,71] In addition to the drugs causing agranulocytosis, sedormid[12] has been a frequent cause of thrombocytopenia. Usually purpura appears suddenly after use of the causative drug for a long period without symptoms but once sensitization is established single doses cause recurrence within twelve hours with the platelets dropping to 20,000.

SPECIFICITY OF DRUG ALLERGIES

The results of observations on the specificity of drug allergies are so variable that no generalizations are possible. This is best illustrated by sulfonamide sensitizations which have been most completely studied. Some patients sensitive to one sulfonamide drug have failed to react to any other members of the group.[36,72,73] Other patients have reacted similarly to sulfadiazine, sulfathiazole and sulfapyridine but not to sulfanilamide.[35,74] Still others have shown sensitivity to all drugs of the group.[49,75] In some instances the sensitization was apparently to the para-aminophenyl radical and reactions were also obtained with sulfanilic acid, para-aminobenzoic acid and procaine.[48,76,77] Park[77] reported that 60 per cent of sulfonamide skin sensitizations were

strictly specific for one drug while Sulzberger[48] found only 10 per cent who failed to show cross reactions. Dowling, Hirsch and Lepper[78] found that 69 per cent of sulfonamide sensitization reactions recurred if the same drug was used again but only 17 per cent if another drug of the group was substituted.

In sensitizations to other types of drugs, instances of both strict specificity and group reactions have been reported. Cooke[79] found that three aspirin-sensitive patients did not react to salicylic acid, benzoic acid, antipyrine, sodium acetate or methyl salicylate. Horsfall's[80] patient, exquisitely sensitive to formaldehyde, did not react to other aldehydes, formic acid or methyl alcohol. Loveman[57] reported a patient sensitive to alurate (allyl isopropyl barbituric acid) who did not react to barbituric acid or any of its other derivatives or to sedormid (allyl isopropylacetyl carbamide). On the other hand, Goodman[81] described a case of a patient with procaine allergy who reacted to all the local anesthetics of the procaine group but not to those of the cocaine, quinoline or pyridine groups. Dawson and Gerbade[82] reported a patient sensitive to quinine who reacted to seven related levorotatory compounds but not to quinidine, the dextroisomer of quinine, or to any of the corresponding dextrorotatory compounds. Patients sensitive to arsphenamine usually react to all the related compounds containing trivalent arsenic but not to tryparsamide in which arsenic is pentavalent. However, there are several reports of arsphenamine sensitization in which the reactions to trial doses of tryparsamide have been the same as those to compounds of trivalent arsenic.[83–85] In a given case of drug allergy only cautious trial will reveal whether other related drugs are tolerated.

DURATION OF DRUG SENSITIZATION

Although few data have been published, it appears that the more severe drug allergies usually persist over a period of years. Cases of aspirin sensitization have been known to last for many years and there are reports of patients allergic to sulfonamide still reacting promptly after one and one half to two years.[86] Robinson[87] reported a patient with arsphenamine dermatitis who remained sensitive after seventeen years. The most striking exceptions to this long duration are the allergic reactions to penicillin which are also exceptional in the frequency with which they subside while the causative drug is continued.[88,89] Patients showing allergic symptoms from penicillin often tolerate a subsequent course after a few weeks or months without reaction.[90,91] At first, these reactions were attributed to impurities which might be present in certain batches of the drug but the same response occurs when relatively pure crystalline penicillin is used. Hopkins and Lawrence[92] demonstrated by skin tests and intramuscular injections that 30 per cent of penicillin-sensitive patients ceased to react within two to twelve weeks.

IMMUNOLOGIC FEATURES OF DRUG ALLERGY

The immunologic mechanism of serum sickness has been described by Longcope, MacKenzie, Rackemann and others and was reviewed by Longcope.[26] When a large amount of heterologous serum is injected into a non-sensitive person, the foreign protein remains demonstrable in the blood for many days; in exceptional cases in whom serum sickness does not develop as long as sixty-three days. Normally, however, serum acts as an antigen and after five to fourteen days, with the appearance of symptoms of serum sickness, a specific antibody demonstrable by precipitin, passive anaphylaxis and Prausnitz-Küstner technics appears in the circulation. During the course of serum sickness there is a gradual rise of antibody titre and a concomitant decrease of circulating antigen, the symptoms subsiding with the disappearance of antigen. After recovery the antibody remains present for months or years, the patient being in a state of anaphylactic sensitization during which time further injections of the same foreign serum produce an immediate violent reaction. This sensi-

tization, induced in normal persons, differs only in details from the spontaneous sensitivity of certain persons predisposed by a hereditary allergic factor in which the *first* dose of foreign serum causes a severe immediate reaction. Both forms of sensitization are readily demonstrable by intracutaneous, scratch or conjunctival tests with the specific antigen.

The anaphylactic type of sensitization produced by parenteral injection of other protein-containing biologic agents is immunologically similar except that, because of the smaller doses and more rapid elimination of the foreign protein, serum sickness does not follow the initial injection into a non-sensitive person. After sensitization is established circulating antibodies are present, although often demonstrable only by the Prausnitz-Küstner method of passive transfer, and reactions to scratch or intracutaneous tests are positive.[28,33]

In delayed urticarial reactions to penicillin, clinically identical with serum sickness, a corresponding immunologic mechanism is not demonstrable. Some authors have reported the presence of positive intracutaneous tests[56,89,93] and skin sensitizing antibodies[93] in such cases but other reports[91,94–97] and extensive studies at The Roosevelt Hospital Allergy Clinic have shown that neither the skin test nor passive transfer is a reliable index of penicillin sensitivity. Small urticarial reactions to skin tests with penicillin may occur in non-sensitive persons and the tests are often completely negative during or shortly after an urticarial reaction. Skin sensitizing antibodies were demonstrable in the serum of less than 10 per cent of clinically sensitive patients and then in such low titres as to be of questionable significance. Also, if the reaction to penicillin occurs more than twenty-four hours after the last dose, the presence of the antigen cannot be demonstrated in the circulating blood as it may in serum sickness. However, it may be assumed that amounts of penicillin adequate for antigenic activity remain in the body during the reaction.

When the typical allergic diseases such as asthma, rhinitis, urticaria and angio-edema are produced by protein drugs or gums, their immunologic features are those characteristic of similar cases due to foods or inhalants. Scratch or intracutaneous tests with the causative agent give immediate wheal reactions and the characteristic skin sensitizing antibody, demonstrable by the Prausnitz-Küstner method of passive transfer but not by the precipitin technic, is present. However, when the same symptoms are produced by crystalloid drugs similar skin reactions and circulating antibodies are only rarely demonstrable. Immediate wheal reactions to skin tests and skin-sensitizing antibodies have been reported to quinine,[82,98] thiamine,[23,24] the sulfonechloramides[20] and sulfonamides[35] but in the vast majority of patients sensitive to crystalloid drugs such tests give negative results and no antibodies are demonstrable. Attempts at such skin tests are not only futile as diagnostic procedures but exceedingly dangerous since severe constitutional symptoms may result even in the absence of local reaction.[99]*

The generally negative results of intracutaneous tests with crystalloid drugs and the failure to demonstrate circulating antibodies apply not only to the allergies manifested by asthma, rhinitis or urticaria but to all types of sensitization by crystalloid drugs. The classical methods of demonstrating antibodies have been developed from studies of protein antigens and are not entirely applicable to allergens of low molecular weight such as crystalloid drugs. The studies of Landsteiner[100] and others, showing that simple chemical compounds when combined with protein might act as haptenes and determine the specificity of antibody reactions, have helped to correlate sensitizations to crystalloid drugs with the familiar protein sensitizations. A number of drugs commonly causing sensitization such as formalin,[101] sulfonamides[102] and penicillin[103] have been

* Many drugs such as morphine, codeine, histamine and acetylcholine produce urticaria in normal skin and so are not suitable for intracutaneous tests.

shown to combine with body proteins and so might act as haptenes. However, the experimental sensitization produced by injecting artificial conjugates of drugs and protein into animals is of the anaphylactic type usually produced by protein antigens and does not resemble the reactions produced by the uncombined drugs in human beings.[101,104] Guinea pigs sensitized by conjugates of sulfonamides with protein react to contact with the conjugate but not to the uncombined drug so the mechanism of the clinical drug reactions is not adequately explained. The use of artificial conjugates of drug and protein in the study of human drug allergy has been limited but so far has not contributed materially to the diagnosis or understanding of the phenomena.[42,105]

A more simple method, adapting the haptene concept to the clinical diagnosis of drug allergy, was suggested by Leftwich.[106] He used sera of patients receiving adequate doses of the sulfonamide drugs (which presumably contained sulfonamide bound to protein) as antigens for intracutaneous tests of sensitivity to corresponding drugs. As a control, he injected serum obtained from the same patients when not receiving the drug. A difference of 4 mm. in the diameters of the test and control wheals was considered diagnostic and results consistent with the clinical evidence of sensitivity were obtained in twenty-eight of thirty patients. Confirmation of these results has not been published. Fink, Burton and Wheeler[107] obtained negative results with the same method in nineteen children and negative results in single cases of sensitivity in adults have been reported.[54,108] Attempts to reproduce the phenomenon in patients known to be sensitive to sulfadiazine, at The Roosevelt Hospital Allergy Clinic, have failed. Intracutaneous injection of normal human serum, even of the patient's own serum, invariably produced a definite wheal and the size of the wheal produced by a serum containing sulfadiazine (blood level 9.6 mg./100 cc.) never differed significantly from that produced by the control serum. This test cannot be considered a reliable criterion for the decision to give or withhold a valuable drug.

Until the demonstration by Landsteiner and Chase[109,110] that the antibodies mediating the reactions of contact dermatitis and tuberculin sensitivity are present in the cells but not in the serum of sensitized animals, the study of allergic antibodies had been entirely confined to the circulating antibodies which are characteristic of protein sensitization. In addition to contact dermatitis, which is a common type of sensitization to non-protein compounds, there is reason to believe that many other drug allergies, for example fixed drug eruptions, are manifestations of tissue sensitivity. The methods employed by Landsteiner and Chase are not easily adaptable to clinical use but it is possible that the further development and utilization of technics for the study of cellular antibodies may demonstrate the immunologic mechanism of many drug allergies in which circulating antibodies are not present. Urbach[111] has suggested that blister fluid contains cellular antibodies not present in the serum.

Further light on the mechanism of contact dermatitis is given by the experiment of Haxthausen[112] who exchanged skin grafts between human identical twins, one twin of each pair being sensitized to dinitrochlorobenzene and the other not sensitized. The sensitive skin transferred to the normal individual lost its sensitivity while the normal skin acquired the reaction of the sensitive host. It was apparent that the skin cells transferred in the graft were not the important repository of antibody.

For purposes of diagnosis, the lesion of contact dermatitis may usually be reproduced by a patch test with the causative agent in a concentration which does not irritate normal skin. Occasional failures may result from the application of an agent producing dermatitis on delicate skin (such as that of the eyelids) to the tough skin of the extremities or back. As has been noted, dermatitis medicamentosa resulting from internal use of drugs has much in common with contact dermatitis and in many such

cases patch tests with the causative agent give positive reactions. These reactions, which may be elicited by such drugs as aspirin, sulfonamides, arsphenamine and penicillin, are frequently helpful in diagnosis but must be considered suggestive rather than diagnostic. A positive reaction obviously depends on the diffusibility of the drug through normal skin but, on the other hand, application of the drugs in relatively strong solutions may expose the cells to much higher concentrations than could result from internal use. Robinson[87] and others have found that the results of patch tests with neoarsphenamine, while often positive in patients who had had arsphenamine dermatitis, were not a reliable basis on which to prescribe treatment.

HISTOPATHOLOGY OF DRUG ALLERGIES

Largely as a result of the studies of Rich,[5] the histologic changes occurring in drug reactions, particularly those due to the sulfonamides, have recently attracted considerable attention from pathologists. Longcope in 1913 to 1915,[113–116] described inflammatory lesions in the kidneys, heart and liver of experimental animals receiving repeated injections of foreign protein. Further studies of experimental sensitization by Klinge,[117] Vaubel,[118] Knepper and Waaler,[119] Masugi and Sato[120] and Rich and Gregory[121] have demonstrated widespread foci of parenchymatous and collagen degeneration with monocytic infiltration and arterial lesions resembling those of periarteritis nodosa and rheumatic fever.

Similar lesions have been reported in patients dying during or after sulfonamide therapy, and occasionally with other types of drugs, without receiving any foreign protein injections. Many of these patients showed clinical evidence of drug allergy, such as drug fever or dermatitis, shortly before death. Rich[5] has particularly stressed the presence of arterial lesions characterized by hyaline and fibrinoid degeneration of the media with perivascular infiltration of mononuclear and polymorphonuclear cells, including eosinophiles, which he considers "typical, fresh lesions of periarteritis nodosa." Similar lesions have been described by other writers,[3,66,122,123] some of whom hesitated to apply the term periarteritis nodosa. These lesions have been described in cases of patients with serum sickness[124] and sensitizations to iodine,[125] thiourea[126] and thiouracil[55] and so are considered a general manifestation of the sensitization reaction rather than typical of the sulfonamides. In addition to these vascular lesions, patients with sulfonamide reactions have shown focal necroses of the myocardium, liver, bone marrow, spleen, lymph nodes, lung, adrenal cortex and other organs, accompanied by focal or diffuse monocytic infiltration which may amount to granuloma formation or extensive interstitial myocarditis.[66,122,123] The kidneys have also shown degenerative and interstitial changes similar to those present in other organs and apparently unrelated to the effects of crystalluria or hemoglobinuria.

The similarity of these changes to the lesions of certain infectious diseases such as typhoid fever, tularemia, scarlet fever, diphtheria and miliary tuberculosis has necessitated careful consideration of the possibility that they might have resulted from infection rather than from the drugs used. Patients suffering from the diseases mentioned have been excluded from the studies cited. In a number of instances, fatal reactions have followed the prophylactic administration of sulfonamides to previously healthy persons with injuries not apparently infected or after operative procedures at which evidence of infection was not noted. In one of Rich's[127] cases, biopsy specimens from the scrotum, obtained five months and again one week before a sulfathiazole reaction, showed no evidence of arteritis which was present in tissue from the same site nine days after the onset of the reaction. Furthermore, in most instances the lesions described have been demonstrated in experimental animals receiving the drugs as well as in clinical material.[122,128]

The belief that the lesion described represents allergic reactions rather than pharma-

cologic or toxic effects of the drugs is based upon several lines of evidence. The lesions attributed to sulfonamides and other drugs are in most cases similar to those found in serum sickness or experimental protein sensitization with typical immunologic findings. When adequate clinical evidence was available, most of the patients in whom pathologic lesions were described have shown typical manifestations of drug sensitivity such as drug fever, skin rashes, arthralgia and asthma during life. The period of administration of the drugs was adequate to produce sensitization but the doses given were not excessive and the degree of reaction bore no relation to the doses used. In many instances, more than one course of the drug had been given and several patients developed reactions from doses smaller than those that they had previously tolerated without untoward symptoms. There is, therefore, good evidence that the histologic lesions are produced by drugs and that they represent sensitization rather than toxic effects. However, as Klemperer,[7] Selye[129] and others have pointed out, these tissue changes can scarcely be considered conclusive proof of allergy in the absence of corroborative clinical and immunologic evidence.

In addition to the lesions mentioned, many writers have considered the massive parenchymal necrosis (acute yellow atrophy) of the liver produced by such drugs as cinchophen, sulfonamides and arsphenamine as a sensitization phenomenon. More, McMillan and Duff[66] considered massive hepatic necrosis due to sulfonamides and the mild focal necrosis, which involved the liver coincidentally with many other organs, as different degrees of the same process and described patients showing intermediate stages of liver damage.

The characteristic change in the bone marrow noted in agranulocytosis due to drugs, an arrest of maturation of myeloid elements at the stem cell stage, may occur in association with the foci of necrosis which are considered a part of the sensitization picture[66] but the relation between the two processes has not been established.

DIAGNOSIS AND MANAGEMENT OF DRUG ALLERGIES

From the discussion of the immunologic features it is apparent that the diagnosis of allergy to protein drugs and vegetable gums can usually be made by means of suitable skin tests but that skin tests and antibody determinations are not reliable in the diagnosis of allergy to crystalloid drugs. Patch tests are frequently of aid in establishing the cause of certain types of skin reactions and positive intracutaneous tests may be obtained with a few crystalloids such as thiamine but usually the diagnosis of allergy to drugs of simple chemical structure must be made on clinical grounds. The most important factor is a knowledge of the diverse manifestations of drug sensitivity, of the symptoms most commonly produced by each type of drug and of the time during the administration when they are most apt to appear. For example, the sudden occurrence of fever, with or without leukocytosis, during the second week of sulfonamide therapy should immediately suggest drug fever and the drug should be discontinued or penicillin substituted. The precautions to be observed with various types of drugs need not be presented here in detail; if the physician is alert to the possibility of drug allergy, a presumptive diagnosis is rarely difficult. Except for the reactions manifested by asthma, rhinitis or urticaria, the drug sensitizations are not notably more common in persons with hereditary predisposition to allergic diseases and the presence or absence of a past history of such diseases is not an important factor in their diagnosis.

The first step in handling any drug allergy is to discontinue the causative drug and in many cases no other treatment is needed although the more serious manifestations of idiosyncrasy, such as agranulocytosis, hepatitis and exfoliative dermatitis, require in addition symptomatic and protective treatment. Occasionally, especially in the case of penicillin, if the allergic

symptoms are mild and the indications for the drug are very strong, its continued administration may be justified but this should be done only with a knowledge of the reactions of the particular drug and with careful observation of the progress of the manifestations of sensitization. The same is true of further use of a drug after the patient has reacted unfavorably in a previous course of treatment. When no acceptable substitute is available, the only reliable index of persisting sensitivity (except in the case of protein drugs) is a small test dose administered by the usual route. It has already been noted that penicillin sensitization is one of the most transitory of drug allergies but at least one death has been attributed to an attempt to use penicillin in a patient who had previously showed evidence of sensitization.[130]

Several authors have attempted to desensitize patients with a drug allergy by gradually increasing doses of the causative drug.[36,51,131,132,133] While the procedure has frequently proven effective in the case of heterologous sera and other protein drugs, the evidence of desensitization to non-protein agents is less convincing. Attempts at oral desensitization of patients with contact dermatitis due to sulfonamides have produced fever and constitutional symptoms, accompanied by marked eosinophilia (leukocyte counts of 16,000 with 62 per cent eosinophiles[51]) which may well have been evidence of serious visceral damage. In the present state of knowledge, the theoretical danger of such a procedure outweighs the evidence of its practical value.

There is some clinical and experimental evidence that the incidence of development of contact dermatitis from the external use of a drug is lessened by the previous or simultaneous oral administration of the same drug.[54,134] The practical significance of this phenomenon has not been developed.

SUMMARY

Allergy to drugs is very common and its manifestations vary in importance from transitory skin eruptions to fatal reactions. Among the symptoms which are considered due to sensitization are not only the usual allergic symptoms of asthma, rhinitis, urticaria and angio-edema but drug fever, leukocytosis, arthralgia, lymphadenopathy and many types of skin eruptions. There is also considerable evidence that hepatitis, agranulocytosis and thrombocytopenia due to drugs are phenomena of sensitization rather than of primary toxicity. In sensitization due to protein drugs, circulating antibodies are usually demonstrable and skin tests are of value in diagnosis. In cases due to the non-protein drugs, antibodies are rarely demonstrated by the usual methods and skin tests, except for patch tests in certain types of dermatitis, are of little diagnostic value. Pathologic studies have demonstrated widespread visceral lesions, chiefly arteritis and focal necrosis, in patients who showed clinical evidences of drug sensitization. The diagnosis of drug allergy depends primarily on a knowledge of its diverse manifestations and of the symptoms most commonly produced by each type of drug. The degree of specificity and the duration of such sensitizations are so variable that generalizations are impossible. Desensitization with protein substances is often successful but the results of similar attempts with non-protein drugs are inconclusive.

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A Working Classification of Asthma

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IN general, there are two ways of approaching the study of chronic disease: In one the investigator selects a few representative cases and then studies these from every possible angle so as to discover and evaluate every deviation from the normal anatomy or physiology which they might display. In the other, the student stands at a distance to try to see the disease as a whole, to compare the "pictures" presented by different groups of patients, to see what these groups have in common one with another and then to see whether the differences between them are real and substantial or whether they are merely variations in the degrees with which the different patients react to this or that aspect of their illness; in other words, to see whether the differences as observed are qualitative or merely quantitative. The fact is that in practice these two ways of approach are not separated too sharply. The "representative case" cannot be selected without some knowledge of the whole disease and groups of patients cannot be evaluated without knowledge of certain details. In his study of asthma so far, the author has devoted his attention mostly to examination of the different over-all "pictures." The fact that he has changed his ideas of classification from time to time is not surprising; it indicates that the problem is not easy and it strengthens his belief that, so far at least, time has not been lost by postponing the intensive investigation of "a few representative cases." To the author a working classification of all the patients who wheeze seems essential. The latest edition of this working classification appears to be so useful, both in the clinic and in the laboratory, that it is presented and discussed here. (Table I.)

A WORKING CLASSIFICATION OF ASTHMA

The asthma which begins before age thirty is a different disease from the asthma which begins after age forty. The picture presented by the "young lady" who wheezes for a day or two when her ragweed hay fever becomes severe is quite different from the picture presented by the "old gentleman" who is "depleted" by the exigencies of a hectic career in business and who finally succumbs to an infection which thereupon precipitates asthma which persists as a chronic, debilitating, serious disease. At the moment of admission to the hospital these two individuals have much in common. They both wheeze and in both this wheeze is relieved by epinephrine. Examination and x-ray in both cases will show the diaphragm low, the lungs distended. In both, the eosinophile cells in the blood may be increased. A "stuffinositis" may be present in both. The immediate pictures are much alike. They both have "asthma." It is the

TABLE I
A WORKING CLASSIFICATION OF ASTHMA

Asthma Begins before Age 30	Asthma Begins after Age 40
"Extrinsic" (Allergy)	"Intrinsic"
Simple	Bacterial Allergy (hard to prove)
Diagnosis easy by history	"Depletion"
Complicated	Psycho—Fatigue
by infections	Somatic
by "depletion"	Infection: Sinuses, Bronchi, Teeth, Other
"Asthmatic Bronchitis"	Malnutrition
Vasomotor rhinitis	(Note Selye's "Alarm Reaction")
leads to asthma (often severe)	"Polypoid Sinusitis"
	Emphysema: Functional, Structural
	Tumors and Foreign Bodies

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over-all picture which varies so widely. The histories, treatment and prognosis are utterly different in the two cases.

When asthma begins before age thirty its cause should be considered as allergy until proved otherwise. By allergy is meant a clinical sensitiveness to some foreign substance, which occurs usually in the form of a dust, but may in a few cases occur as a food or, rarely, as a drug. The symptoms develop because of the reaction which results when the patient makes contact with this foreign substance. The great majority of young people who develop asthma before age thirty will tell in their history that the asthma occurs only at certain times of year and/or only in certain particular environments. Some of them know that their asthma is merely a complication of hay fever and all they want is treatment to prevent the next season's attack; others know that cats, dogs or horses are intolerable and they, too, want protection against attacks which occur in odd places and at odd times to make life a burden. Other cases, however—and they constitute the great majority—are not aware of their allergy. It is only when the physician unravels the long story by noting the dates and ages when each and every attack began and when it ended, and by noting at the same time the relation of attacks to changes in residence, in occupation, or perhaps to the time of year, that the nature of the process becomes clear. As the table says "diagnosis easy by history"; it should be easy but there are tricks in history taking and the physician who would treat asthma must be a detective as well as a doctor.

This simple allergic process may become "complicated." In many cases the attack continues after exposure to the foreign substance has ended. Secondary infections are the common factors; a pharyngitis or sinusitis can cause the symptoms of a ragweed hay fever to continue into late October, past the time when the simple cases have cleared. An infection can make the attack started by the visit to grandma and her cat hang on for a week or so after the boy has returned to his home. "Depletion" by itself and without clear evidence of infection can complicate a simple allergic asthma, but that will be discussed later. In all these cases in which allergy plays such a vital rôle it is the clinical history which reveals the cause of the trouble. Skin tests usually confirm the history; but if they remain negative when the patient ought to be sensitive, the history should be the guide, at least until proved to be wrong. The reason for this is that skin tests which are negative at first may become positive later. The sensitiveness of the skin may or may not reflect the sensitiveness of other tissues. In a few difficult cases the finding of skin tests positive to substances chosen at random will suggest some new factor the importance of which will be disclosed by further history and observation. In general, one can say that in the young extrinsic cases the theory and mechanism of allergy provides an adequate explanation of the clinical pictures observed: It makes sense!

"*Asthmatic bronchitis*" is a designation which is useful for it applies to a goodly number of cases. The term has been used too loosely; it should apply to those cases only whose asthma comes in isolated attacks at long intervals apart and without change in the home or occupational environment, the attacks being precipitated by head colds and bronchitis. The two words indicate the mechanism. The new infection—the "bronchitis"—not only starts the process but it alters the sensitiveness of the individual. Why do these people wheeze with their colds? Is it not because the new infection lowers the threshold of reaction to make a slight degree of sensitiveness or allergy become effective enough to cause clinical symptoms? The support for such a theory comes from the considerable number of patients, especially young people, in whom it seems to apply. Also, the results of treatment fit the theory. When the general health can be improved so that resistance to new respiratory infections is increased, then the attacks are prevented. The rôle of allergy—the "asthmatic" factor—is demonstrated by

a number of cases in which removal of the offending factor, the cat, the feather pillow or the cosmetic, resulted in the removal of the "asthmatic" factor. New colds persist as usual but now there is no wheeze to go with them. In occasional cases specific treatment to desensitize the individual against the particular foreign substance—cat hair or dog hair, for example—will modify his reaction capacity to a considerable extent. The author must acknowledge that proof of the theory that the threshold for allergic reaction can be lowered in various ways has not yet been demonstrated by animal experiments in the laboratory. Present support derives entirely from observations in the clinic. The treatment of asthmatic bronchitis is not always easy.

Vasomotor rhinitis leads to asthma. There is a small number of patients who develop a chronic vasomotor rhinitis in their twenties; most of them are women. Evidence of allergy is not to be found; the symptoms are remarkably persistent, bearing no relation to changes in season or environment, and skin tests show no reaction to any common food or dust substance which will make sense with the history or with the subsequent experience with that patient. For some time, usually several years, the nasal symptoms continue in a peculiarly distressing manner and then quite suddenly asthma develops and, like the nasal symptoms, this asthma is persistent and is often severe. As a whole, these patients are hard to deal with; no treatment is really satisfactory and in some the asthma goes on until it becomes intractable. One or two of these patients, young women in their late twenties or early thirties, have died in status asthmaticus and at autopsy have shown the typical pathological condition of death from asthma with the bronchi occluded by tough, sticky exudate and the lungs distended. Whether this general picture represents a separate disease or whether it is merely an exaggeration of other more common types of asthma is uncertain. The subject is important and requires much further study.

When asthma begins after age forty the cause is not allergy unless proved otherwise. Allergy is a disease of youth. The age at which typical allergic asthma begins and the age at which typical ragweed hay fever begins is usually around age twenty. After that the curve which summarizes the ages of onset falls off until after age forty; there are only a few individuals who begin their symptoms at an older age. The "old gentleman" is not affected by changes in environment, at least so far as specific dusts are concerned, and he is not sensitive to any particular food. Whatever the cause of his trouble, it is something which he carries with him. Unlike the "young lady" whose asthma clears promptly after admission to the clean and relatively dust-free hospital ward, his asthma continues; his response to treatment is slow. What is the nature of this disease which is "intrinsic" in so far as the cause is "inside" the body?

Infection plays a part but this varies and, as will be seen, the evidence of infection is not clear in many of the cases. "Bacterial allergy" is the obvious concept but it is hard to prove. Skin tests with bacteria and their products, like toxins or vaccines, will elicit positive reactions but these are, like the tuberculin reaction, delayed in appearance and inflammatory in nature. Like the tuberculin reaction, they indicate that this individual has or has had infection with the organism. As with the tuberculin reaction itself, the test finding has little practical significance except as an interesting item to be evaluated in a few cases under special investigation. Such skin tests do not help in the study of asthma. In contrast to tests with toxins and whole organism suspensions (vaccines), the specific soluble carbohydrate substances derived from the capsules of certain bacteria can elicit a skin test of the immediate, urticarial wheal and erythema type. This occurs, however, only when antibodies for the organism are present in quantity. It is possible that further studies with specific bacterial carbohydrates will be helpful; the problem will be concerned with the relations between the skin results and the state of the

asthma, a study of immunology involved. It may be that bacterial allergy can be defined and found to be important.

"*Depletion*" is a factor in the cause of asthma which has more than casual importance. The toxins arising from a focal infection can perhaps cause a tissue injury to make the cells release histamine and so cause asthma by a mechanism comparable to that of the antigen-antibody reactions. The case for chronic infections is understandable. The case for certain intoxications, as with sulfonamide drugs, is also understandable. Other conditions, however, like malnutrition, improper hygiene and, in particular, the larger group of psychic disturbances which are so poorly defined are not so easy to correlate with the other pictures of asthma due to more orthodox causes. Do they also produce asthma through tissue injury and histamine release? There is evidence to indicate that this happens but it is not clear; the problem needs much more study.

Selye's conception and investigation of the diseases of adaptation is pertinent to this problem even though some of the physiologic changes—the fall in blood chloride, for example—which he finds after injuries is not found also in our patients with severe asthma. Whether the discrepancy depends upon quantitative rather than qualitative factors, or whether the chronic shock-like state which develops after injury finds its counterpart in the depletion of severe asthma remains to be disclosed. In this latter case the depletion is the result of the process. It is our clinical observations which point to the fact that depletion started perhaps by a primary injury either of the soma or of the psyche that may be the cause of the process.

Can "depletion" of one sort or another cause asthma without allergy or without infection of any kind? That is the important question and again it is clinical observations which have provided the basis for the answer. It is the end results of treatment prescribed and administered on a basis of depletion rather than of allergy or infection which indicate a true cause and effect relationship. Figure 1 shows a sample of twenty-three patients with intrinsic asthma who have been "cured." The sample has been taken at random; the cases are not selected on any basis except for the final "cure." The figure shows that "cure" may persist for ten years or more but it is the method of cure as evaluated by both doctor and patient which is the important item. In some cases treatment with potassium iodide or the removal of bad teeth has explained the "cure" and that of course does indicate infection; but when asthma clears when the bad hygiene is improved or when the malnutrition is corrected by proper feeding, and especially when it clears after the elimination of psychic difficulties—"the divorce was finally arranged"—one has to recognize that the problem includes other factors beside allergy and infection. The author finds that these cases are common. It is in these cases that treatment of the patient is so much more important than treatment of the asthma. There is much to learn about psycho and psychosomatic factors in this chronic disease.

Polypoid sinusitis with asthma is given a separate heading chiefly because the patients to be included are such a large group. Lesions of the nose and sinuses are noted in three places in this classification. The chronic vasomotor rhinitis which develops in young women has been mentioned. Some of them have polyps, an extension and result of the chronic irritation of the sinus membranes. In chronic intrinsic asthma, occurring in older patients, polypoid sinus disease is common; it is found in about one-third of all the cases and the typical subjects are grouped in this special designation. Operation on the sinuses does more harm than good, except in a few "lucky" cases, and it is interesting to speculate on these few. Under the heading "Depletion," Table 1 indicates infection of the sinuses as one of the subgroups, and in so doing it implies that treatment of the sinusitis by operation and removal of the focal infection has brought relief to the

asthma. Can we say, therefore, that chronic infection of the sinuses does occur, but only in a few cases, and that in the other group which is much larger the polypoid sinusitis represents a part of the picture and not a cause of it? When in earlier days these other patients were operated upon, the cultures taken from the sinus content, a thick white mucoid material, often showed no growth. The author recalls the autopsy of a patient whose frontal sinuses were opened from above through the base of the skull and the cultures showed no growth. How to distinguish the few cases in which drainage of the paranasal sinuses will relieve the asthma permanently from the vast majority in which similar treatment will make the asthma worse (after a very temporary benefit) is one of the pressing questions.

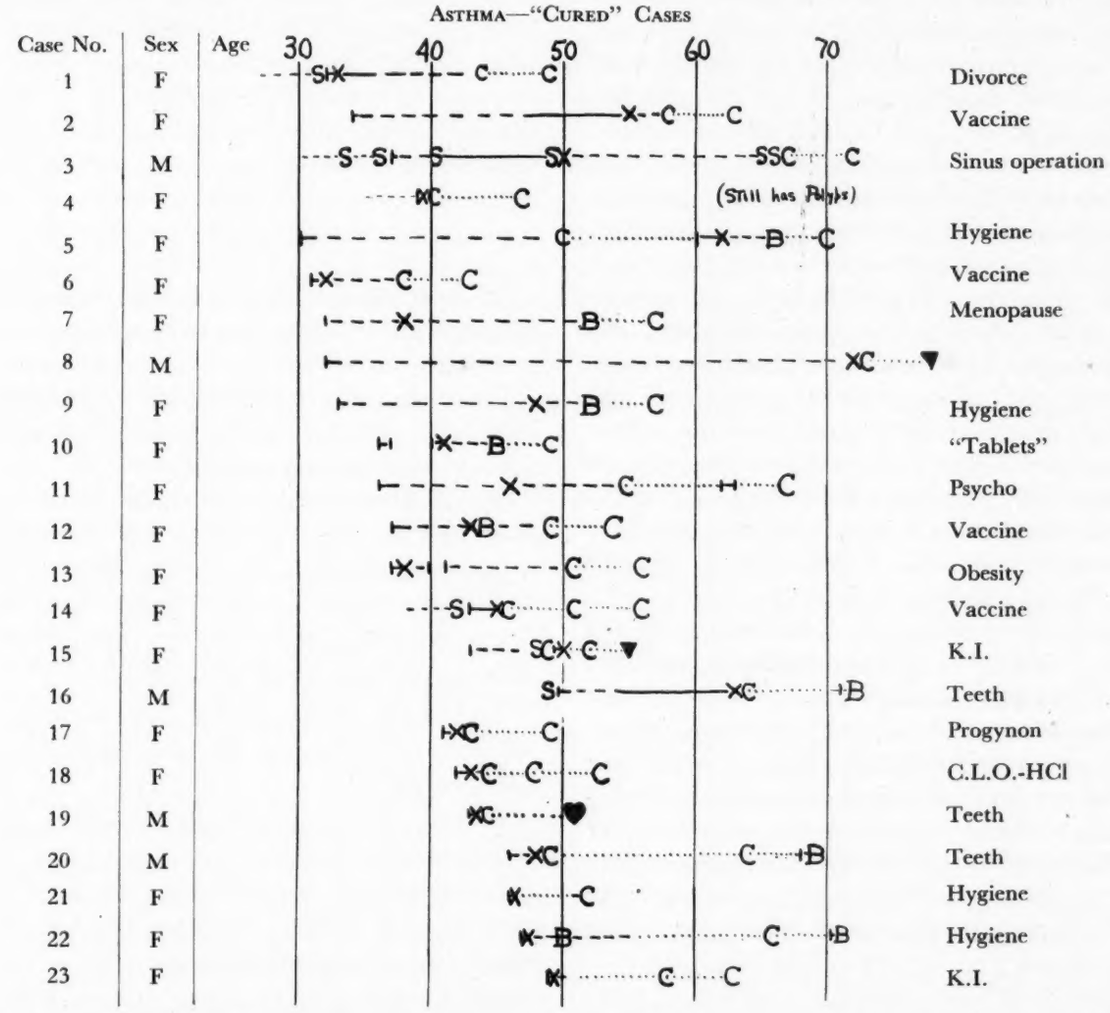

Fig. 1. A random sample showing twenty-three cases of "cured" asthma is presented to show the general method of study. Each line represents the life history of the patient's asthma. On the left, a vertical mark indicates the age at which the asthma began and the dashes or the continuous line show whether this asthma was in attacks or was persistent. Symbols in the line indicate as follows: "X" marks the first visit of the patient to the author; "B" means better, the asthma under control. "C" means cured, the patient free of asthma without treatment and the dotted line after "C" or sometimes before it indicates the duration of this "cure." New letters, whether "B" or "C," indicate a new follow-up report. "S" means sinus operation which sometimes, as in cases 1, 3 and 14, was made before and not after the onset of asthma. In cases 16, 20 and 22, the asthma recurred at about the age of 70 but the "B" indicates that it was not severe. The black triangles indicate death from causes other than asthma. The black heart indicates death from coronary occlusion. The circles around the small initials in the left column indicate the men; there are five men in this list. The words in the right hand column indicate the method of "cure," as explained in the text.

Emphysema causes wheezy breathing (asthma). Every attack of asthma, no matter what its cause, is accompanied by a "stretching" of the lungs; the chest enlarges, the diaphragms become flat and low and their movement is restricted. The vital capacity falls off. As the attack passes, the emphysema passes also; it is a purely functional emphysema. Structural emphysema is probably a definite disease entity. It has been called idiopathic because it develops without cause, insidiously in older people and more in men than in women. It is a slowly progressive disease and has a poor prognosis. The victims do not survive for more than a few years. Physical examination shows changes much like those of chronic asthma and the diagnosis depends more on the history and the subsequent behavior. The relation to exertion is always sharp. At rest the patient is reasonably comfortable but his tolerance for exercise is small. A point of diagnostic importance is that whereas the patient with asthma has bad nights, "emphysema sleeps well." Mention of the disease is included here because it happens not infrequently that patients with structural emphysema are put through the asthma routine, with skin tests to many different substances and sometimes treatment with dust extracts and other materials. The fact that such treatment does no good is not surprising; it reflects the lack of training and insight of the attending physician.

Tumors and foreign bodies must, like emphysema, be mentioned in every survey of the asthma problem. Adenoma or carcinoma of the bronchus, gumma of the trachea, Hodgkin's disease involving the peribronchial lymph nodes and sarcoid have all been seen by the author in patients who were thought to be asthmatic. Merely to think of these possibilities is usually enough to rule them out but it is important to think of them.

SUMMARY

1. A working classification of some sort is essential for the study and treatment of asthma.

2. When asthma begins before age thirty, it should be considered to depend upon allergy until proved otherwise.

3. When asthma begins after age forty, it should be considered as due to factors other than allergy until proved otherwise.

4. In the younger age group it is the clinical history which is of vital importance in diagnosis and so in treatment.

5. In the older group the factors of "depletion," both psychic and somatic, may be essential.

6. Polypoid sinus disease is more a part of the picture than a cause of it.

7. Structural emphysema as well as tumors and foreign bodies must be considered in all difficult cases.

Recognition of Emotional Factors in Allergic Manifestations*

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THE literature relating to causes of allergic reactions refers not only to specific causes but also makes constant reference to non-specific causes, under which are grouped most prominently "worry, nervousness and fatigue." The frequency with which these non-specific causes are mentioned and the generally acknowledged rôle that they play, not only in precipitating and aggravating allergic reactions but even at times acting as sole causative agents, suggests that a closer survey and appreciation of the patient's history would prove fruitful, particularly if attention is directed to the emotional and environmental circumstances under which the allergic disorder first became manifest. In many instances, a striking correlation will be found between the onset of subjective complaints and a single psychologic event or series of such events. Conversely, the remission of allergic manifestations may also coincide with the occurrence of severe or disabling emotional experiences. It is of at least empiric value that the Quarterly Cumulative Index Medicus for the past ten years contains articles attributing specific curative properties to a multiplicity of unrelated drugs and equally unrelated procedures. The only common basis upon which these claims may be said to achieve their results is their common suggestive value or perhaps the faith that the patient has in his particular allergist.

It is incorrect to assume that the taking of a psychiatric history is the exclusive right and privilege of those engaged in psychologic medicine. This misconception, which is widely held, stems from the intensive specialization in the increasingly numerous branches of medicine. The medical profession seems to have progressed to the point where it now resembles the many factional units of a complex labor group. There is no valid reason why history taking should rigidly avoid obtaining an account of the personal and intimate history of the patient in terms of psychologic events and integrating these events with the somatic reactions which occurred at the time. There is no longer any doubt that when the physician combines the physical approach to a problem with an appreciation of emotional factors he establishes with the patient a contact or rapport which has great therapeutic potentials. This rapport, once established, is sometimes sufficiently strong in itself to alleviate distressing symptoms and on occasion it has positive curative value. For example, the allergist who is convinced by his own faith in the efficacy of his particular mode of therapy not infrequently is so forceful and energetic in his approach to the patient's problem that an alteration may take place in the patient's underlying emotional conflicts. The immediate improvement in the patient's condition is then attributed to a specific administration rather than to the personality of the administrator. The results thus achieved may possibly explain why the faithful exponents of foods as allergens, house dust as an allergen or even sodium chloride as an allergen are so vigorous in supporting their respective claims in the universality of their treatments.

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By placing prime importance upon the history of the patient's family (rather than upon his personal, psychologic history) and searching for clues of related allergic manifestation in members of his immediate and remote family the allergist emphasizes his primary interest in the fact that allergic disorders are more commonly found in individuals who are constitutionally endowed with physical properties susceptible to specific allergens. From a psychiatric point of view it is proposed that the manner in which the patient's combined psychophysical makeup will respond to various emotional factors will depend upon the extent to which such factors are similar to or in common with those in the patient's particular emotional environment. If this point of view is kept in mind in history taking, it will be necessary to give equal consideration both to inherited intrinsic antibody-antigen reactions and to the patient's emotional reactions to everyday living and activity. It would be unfruitful at this level of knowledge to argue the relative weights and values of these respective elements. In fact, it does not make much difference so long as we bear uppermost in mind the welfare of the individual who is almost constantly distressed by his annoying symptoms.

The personality of the allergically susceptible individual is commonly characterized by emotional immaturity, relative passivity and need for dependence upon some authoritative yet kindly person. The reactions of this type of personality are thus essentially infantile. It is misleading, however, to assume that these traits are characteristic of and peculiar to the allergic individual alone for similar traits are also recognizable in gastrointestinal neuroses and are common in the chronic alcoholic. In view of these widely divergent physical reactions in relatively similar types of emotionally immature persons, it would appear that the choice of physical reaction to an emotional situation bears a relationship to the patterns of living and behavior of the parents of the emotionally immature individual as well as to his physical makeup.

The outstanding and provocative elements that give rise to many if not all adult maladjustments have their origin in the interaction of the various members of the family unit. The child's position in the family constellation is constantly threatened by anxiety-provoking situations. The rivalries and resentments common to everyday competition in the home create an emotionally conflictual situation. French[1] has shown that when the conflictual situation involves a threatened or actual loss of love of the mother, or the mother-substitute, the patient responds in a physical way compatible with his inherited constitutional endowments. An example is the often repeated observation that asthma is apparently hereditarily transmitted from the mother. The adolescent, or the patient in a state of emotional turmoil, identifies himself with the mother and behaves in a manner similar to the mother's behavior in order to ward off the threatened withdrawal of love, dependence or the threatened loss of security. It is acknowledged without question that sensitization is transmitted but the point emphasized here is that the sensitization can be utilized for the physical expression of an emotional situation. The behavior of the patient may be characterized by the statement that the emotional tension is expressed in "allergic language."

The trying emotional situations that confront the adolescent or the adult are merely repetitions, in a more complex form, of the same problems that confronted the individual in childhood. The failure to achieve scholastic recognition, the frustrations of a competitive occupation or profession or the threatened dissolution of a marital union are but a few of the many problems that were encountered in a simpler form during the period of childhood development.

It may be judged from the type of material seen in a general psychiatric practice that the allergist, in following a limited restrictive type of therapy and searching for a specific sensitization, is frequently led astray by his contact with a group of symptoms simulating an allergic disorder.

When no results are forthcoming, the symptom complex is given the euphemistic title of "intractable allergy." It is just this group of disorders in which the provocative factors are most frequently of an emotional character and in which the major, if not the sole, approach should be from a psychologic level.

Particular mention should be made of the frequency with which hyperventilation with its protean manifestations, either in the presence or absence of allergic sensitization, produces a clinical picture that in many instances defies differentiation from an attack of allergically induced asthma.[2] The anxious, tense, emotionally immature individual is intensely susceptible to changes in his acid-base equilibrium and the outstanding clinical symptom is an inability to breathe. This inability to breathe is predominantly inspiratory and the suddenness of the onset, the complaints of panic and wild gasping for breath may be and often are mistaken for signs of an asthmatic attack. It has been demonstrated that the hyperventilation phenomenon, aside from a few rare instances, is induced by emotional conflict. The management of hyperventilation by a technic other than psychologic then only leads to a state of chronicity and invalidism.

CASE REPORTS

CASE 1. M. H., a twenty-six year old, white, single engineering student was referred for psychiatric consultation and treatment in December, 1945. The complaint was "disabling headaches" of six years' duration. A usual attack was ushered in by a sharp, boring pain, beginning on either side of the head and later spreading over the whole head and then radiating to the neck, both shoulders and down the spine. Vision became progressively blurred and scintillating lights appeared when vision was practically nil. Nausea and vomiting followed and these were accompanied by anxiety and a vague feeling of guilt. Complete isolation in a darkened room for twenty-four hours usually cleared an attack but the patient would not fully recover for ten days or two weeks at which time there would be a recurrence.

The patient's symptoms first began to appear in September, 1940 when, while watching a football practice game, he suddenly felt "hot all over," became tense and apprehensive and then his heart "began to pound." This episode lasted for about thirty minutes and that evening he was nauseated. Two days later, while at a movie, he had a similar attack. For a period of a month thereafter he was entirely well until, again at a football game, he became nauseated and had the first of the headaches described.

The results of the physical and neurologic examinations were negative. The usual laboratory procedures, including x-rays of the chest, head, spine as well as the electrocardiogram, revealed nothing unusual. The pneumo-encephalogram showed an incomplete filling and ventriculograms were therefore obtained. The results were considered normal. All types of medication were seemingly of no value in giving any degree of subjective relief. With a family history of migraine in the mother, the patient was referred to an allergist whose physical findings were essentially as stated. He put the patient on an elimination diet. After two and one-half years, during which time he lost 35 pounds, his headaches were about the same in frequency and intensity.

On the recommendation of his physician, he was excused from selective service and went to work in Alaska on a construction project. Away from home for a period of two years, he had only occasional attacks. Upon his return he was advised to give up his plans for an education and take up an occupation in a colder climate.

A more detailed psychiatric study revealed that he was the eldest of four brothers, the youngest of whom was then twelve years of age. The mother outwardly affected a calm and serene disposition but in their home her attitude toward the father bordered on despotic tyranny. The father, chronically alcoholic, was totally neglected by the family and when he attempted to exert authority, generally in a drunken rage, he was simply placated. One form of overt punishment of the father by the mother consisted of periodic headaches that had been diagnosed as migrane. As early as at the age of ten years, the patient utilized transient "sick headaches" not only to maintain his position with the mother in competition with his brothers

but also to immobilize any anger emanating from the father.

At the age of sixteen, he was instrumental in separating the mother and father who were in a violent quarrel and in the argument the father turned upon the patient, administering a brutal beating. The patient stated that he was choked until he thought his eyes "would pop out of the head." Several days later, he awakened from a sound sleep in a very anxious, tense state and "was unable to breathe." Detailed accounts of this "attack" were highly suggestive of prolonged hyperventilation. It was concluded that these physical symptoms set the pattern for his later so-called migraine. To substantiate further this conclusion, the patient was overbreathed for 90 seconds and all of his physical symptoms, accompanied by great apprehension, were reproduced.

Further discussions clarified his intense and almost infantile dependence upon the strong-minded mother. His reactions toward his psychically weak father were those of hate and resentment, both accentuated by the beating his father gave him. In time, his attacks of headache became related to other emotional situations characterized by violence, for example, the football games. He has had no headaches for the past six and one-half months. He has returned to school and is living at home with his mother, father and brothers.

Case II. R. F., a forty-year old white, married man, who is a general merchant, was referred to the University of California Hospital in April, 1944, for a study of his recurrent, generalized urticaria and angioneurotic edema of two years' duration.

He had lived his entire life in the same township. The routine history revealed no significant factors in his family background or past history.

He was perfectly well physically until April, 1942. He awakened one morning to find his chest covered with "itching hives" about 2 inches in diameter. That same afternoon his eyelids and lips began to swell so that by evening he was hardly recognizable. Sometime during the night all of the manifestations disappeared. Intermittently, he had similar attacks as often as four times weekly and at the time of his hospital entry the urticaria was generalized. He had recognized the fact that emotional situations aggravated an attack and for this reason he had begun to live the life of a recluse.

Prior to admission to the hospital he had consulted several physicians with little or no relief. Apparently, no extrinsic or intrinsic allergic factors were implicated although in one test he was found to be sensitive to corn, peas and grapes. Subsequent tests did not confirm the sensitization. A barrage of medications, including sulfa drugs and penicillin, were used to no avail.

After reviewing the history with the patient the direct question was asked: "What do you think causes your hives"? After some hesitation the patient responded: "These things seem to come on when I get a funny tight feeling in my throat. I get this feeling when I am around my wife, and that is why I stay away from her and the children as much as possible."

In further discussion of the so-called "negative family history" several interesting points were uncovered. The father had died before the patient's birth. He had one brother ten years his senior. His relations with his mother and brother were, to the best of his knowledge, quite amiable until his brother, by legitimate means, took over the controlling interest in the family enterprise. Although the mother was quite complacent, the patient bitterly resented the arrangement and forthwith severed himself entirely from his brother, urging his mother to do likewise. "At least I wanted the satisfaction of caring for her myself," he said.

His mother died when he was twenty-four years of age and one year later he married. In 1939, at the age of thirty-five years, he became associated with his brother-in-law in a business venture that proved highly successful. Some time later, the patient was confronted with certain financial irregularities of the brother-in-law. The patient's wife tended to protect her kin and urged the patient to let it "blow over." From this time on he became increasingly irritable, restless and nervous. He tried to rationalize his nervousness, ascribing it to problems of labor, the war and minor disagreements in the home. In April, 1942, he had his first attack of hives.

When attention was called to the "funny tight feeling in his throat" and his unexpressed hostility toward his brother-in-law, he volunteered the statement that his unhappy relations with the brother-in-law were identical with those he had with his own brother. The relations with his mother, his obvious dependence upon her and his subsequent equivalent dependence on his wife were left undiscussed.

He was in the hospital for six days for observation only and to date has had no recurrence of any urticaria.

CASE III. G. L., a sixty-year old white, married man and business executive, was first interviewed in December, 1944. In 1921, he had his first attack of hay fever and since 1931 had suffered from recurring attacks of asthma. At various times, he had been found sensitive to approximately thirty different pollens, particularly that of Bermuda grass, foxtail and velvet grass. When he originally sought help for his asthmatic attacks, an examining physician on May 26, 1931 noted "worry and nervousness. ++++" The results of the general physical examination and of laboratory tests in 1944 were negative with the exception of the sensitizations just mentioned.

The patient's medical history disclosed that the first treatments aiming at desensitization were poorly tolerated and that after an interval relief was found from "Doctor Tucker's Asthma Specific." In time, this preparation lost its effectiveness and then followed a period of ten years of alternate trials at desensitization and elimination diets. At the patient's own request, he was finally sent to a psychiatrist for an evaluation of his "nervousness."

Given the opportunity, the patient proved most cooperative. In great detail, he gave an account of his most unhappy early childhood. He was the only child of an aged couple. His father, a ruthless, domineering and exquisitely puritanical minister, was forever dwelling upon the wickedness of mankind and the potential sources of evil in his son. The mother vacillated from moods of serenity and compassion, on the one hand, to ominous, threatening domination on the other. He remarked: "I could never know what side of the fence she was on and until her death I was out of breath trying to keep up with her."

From early childhood his feeling and actions had been patterned in accordance with his mother's more sublime wishes. At the age of twenty-two he fell in love with a distant relative and when he sought permission to advance his courtship, he was rebuked and discouraged by his mother's remarks that his offspring would be idiots. In striking contrast to the mother, this girl was soft, docile and "angelic." The disruption of this love affair gave rise to a group of symptoms associated with hyperventilation which, at that time, was interpreted as "a touch of asthma." The family moved and the so-called asthma cleared.

His marriage at the age of twenty-five was the culmination of an arrangement managed by the mother. The marriage as a source of physical companionship was reasonably successful. As a source of warmth and affection it was a dismal failure. His wife, possessing the agressiveness of his mother, pushed him into a most lucrative position.

What precipitated his hay fever in 1921 is unknown but the onset of the asthma is definitely related to a visit with the girl of his first love affair. She at that time gave an account of her own unhappy marital experience, described her continued attachment to the patient and pledged unremitting affection for him. Several days after her departure his asthmatic attacks began.

The history was told with a great display of emotion and it was easily recognizable with interpretation that the patient had great dependence upon his earlier love. The importance of the emotional element was further demonstrated by the fact that by merely telephoning or writing to her he had been able to ward off attacks. Of particular interest is that these attacks of asthma were allergically determined; nevertheless, in two and one half years he has had but two attacks and these were treated without resort to adrenalin.

CASE IV. R. E., a thirty-two year old, white, married woman was referred to the University of California Hospital in March, 1939 for psychiatric evaluation. The referring internist was impressed by the patient's behavior in the presence of her mother who had come with her and who seemed more distressed than the patient by the asthmatic attack of which the patient complained.

The patient had been under continuous medical care since she was ten years of age. She had had contact with innumerable allergists throughout the country and had been subjected to every conceivable medication and procedure, including residence in an air-conditioned home prepared at great expense. Her asthma was truly "intractable." The internist had been the first to evaluate accurately the emotional factors involved and, because of the complexity of the situation, the patient was referred for further investigation. In the several contacts the internist had had with her, he had been able, by his interest, to control several of her attacks without medication. At the same time, it was recognized

that she had an allergic susceptibility to certain pollens and foods, particularly eggs and wheat.

The earliest memories of the patient center about an experience at the age of five. As a consequence of disobedience, she said: "I was spanked by my father until I cried so hard that I lost my breath. To bring me back, my mother turned the garden hose full force in my face." An earlier significant event was related by the mother who stated that when the patient was one year old the coughing paroxysms of whooping cough were so severe "that I had to hold her by the ankles and slap her buttocks to start her breathing again." The patient's first attacks of clinical asthma took place after a series of strenuous exercises. At this point her medical history began.

Many pertinent emotional factors were evident in the family history. The mother and father never enjoyed a real degree of harmony. The mother's affections were expended exclusively on an only son sixteen years older than the patient. The patient can readily recall the often repeated remark that she was unwanted and that she resembled her father in personality and temperament. When she was twelve years old, her brother, then twenty-eight years of age, was killed accidentally. The mother, after a period of mourning, reversed her previous attitude toward the patient and showered her with affection so that "mother and I became very close and people remarked on her devotion to me." The attacks of asthma were thereafter less frequent and less intense until her marriage at the age of sixteen to a close associate of her brother. She remarked: "My mother was very pleased with the marriage, but almost overnight my asthma returned in full force."

The patient's premarital plans included recognition of the husband as a central figure in the household but this plan was short-lived since the mother joined the couple on their honeymoon insisting that "sex was the root of her asthma." It is striking indeed that in those instances when separation from the mother was enforced the attacks of asthma were greatly diminished and at times were absent.

The psychiatric discussions brought out the marked dependence on the mother and the equally strong tendency to achieve a degree of independence of her mother. The struggle between these two opposing drives was satisfied to the extent that the patient retained her mother's affection and at the same time endeavored to punish her mother for her ruthless domination by having the asthma attacks. The patient has been entirely free from attacks of asthma for eight years. During the war years she resided with her mother and since her husband's return from service relations with the mother continue to be amicable.

COMMENTS

Clinical case histories, as reported here, are open to several criticisms. Obviously, the material is selected to demonstrate the purpose of the thesis, namely, the importance of adequate history taking with reference to the emotional factors that are operative in allergic manifestation. Dratler,[3] in a critical review of the problem of urticaria published in 1946, states that "the most important source of information for the determination of etiology is the history." He continues: "All authors have stressed that the patient's experience and observations should be more valued than the skin and laboratory tests." To the extent that psychogenic factors are concerned Dratler states that "the psychogenic element is considered as one of the most important factors in etiology." In another recent paper, Harris[4] gives an entirely different appraisal of the emotions when he states: "In recent years, an old theory and one that most of us considered long ago discarded, namely, that bronchial asthma is a form of neurosis, has been renewed." Harris, with many others, assumes that the emotional turmoil is a natural consequence of an allergic disorder but there is much evidence to question this assumption.

Another criticism is that the diagnoses are in error in that these individuals are "simply neurotic." In this regard, the diagnoses in all the instances cited were made by allergists who treated the patients without success by their restrictive and circumscribed type of therapy. Two of the patients were treated to the point of financial insolvency.

A third possible criticism is that psychiatric interviews are non-scientific and are lacking in specificity in that the therapeutic

results cannot be adequately measured and appraised by rigid scientific standards. However, it seems impractical to await the complete understanding of the mechanism whereby emotions influence bodily function before utilizing the psychiatric approach. In overlooking the emotional components while searching for a specific remedy we are indeed inconsiderate of the patient. Bowman's[5] remark regarding the neurosis applies equally well to most, if not all, physical diseases: "Treatment should be based on securing the maximum results in the shortest time with the least amount of suffering for the patient."

CONCLUSION

It is concluded that if history taking is broadened to include the psychologic events of the patient's history and if these events are related to the somatic reactions at the time of occurrence, the rôle of the emotions in causing, precipitating and aggravating latent allergic sensitization will be adequately recognized and the study, diagnosis, treatment and cure of allergic manifestations will be substantially furthered.

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Allergy in the Nervous System*

A Review of the Literature

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IN recent years an increasing tendency has been noted in neurologic clinics and meetings to ascribe to allergy an important rôle in the etiology of measles encephalitis, scarlet fever encephalitis, multiple sclerosis and some other nervous diseases. Especially in those forms of encephalitis in which there is loss of myelin, an allergic reaction of some kind has been suspected as the common factor producing the break-up of the myelin sheaths.

CLINICO-PATHOLOGIC STUDIES

Osler,[2] in 1889, added the third case of hemiplegia following vaccination, giving credit to Heine[1] in 1860 and Wuillamie in 1882 for reporting the first two. In addition, Osler noted that cerebral palsies "may follow any of the specific fevers." According to Pollet,[9] Englemann[3] in 1897 noted peripheral neuritis following the use of serum and Gardere and Gangolphe[4] noted neuritis during the treatment of a case of tetanus by serum therapy in 1908. Optic neuritis during serum sickness was observed by Mason[5] in 1922. May[6] in 1923 noted attacks of unnatural somnolence of anaphylactic origin. Sternberg[27] also drew attention to seasonal somnolence as a possible form of pollen allergy.

In 1926, Kennedy[7] suggested that acute perivascular edema of the brain may play a part in some of the malignant types of insular sclerosis. In 1926, Duke[8] suggested that peripheral nerve lesions may result from food allergy. Hurst[29] gave credit to Glanzman[10] as the first to suggest, in 1927, that allergy might be a factor in causing demyelination of the nervous system.

Kennedy[11] in 1928 reported meningeal and focal brain disease causing hemiplegia, aphasia, hemianopsia and severe papilledema during the course of serum sickness. Allergic headache due to food was reported by Eyermann[12] in 1930. A case of polyneuritis due to typhoid vaccine was reported by Dr. Geo. H. Hyslop and was described by Kennedy[11] in 1928. Typhoid vaccine and staphylococcus vaccine were also reported by Young[13] in 1932 to cause peripheral neuritis. Winkelman and Gotten[15] reported two cases, one with autopsy findings of encephalomyelitis following the use of serum or vaccine. The autopsied patient had received horse serum seventy-two days previously but had also had symptoms of an upper respiratory infection three weeks later. At autopsy there was inflammation with lymphocytes in the meninges and about blood vessels, especially in the spinal cord, with obliteration of the gray and white matter, congestion and an increase in astrocytes. There also was degeneration with focal necrosis and Gitter cells especially in the cerebrum. Gayle and Bowen[14] reported the case of an eighteen year old boy who developed an acute ascending polyneuritis following the administration of typhoid vaccine and condensed the available autopsy reports in the literature suggesting the following fundamental lesions: peripheral neuritis, destruction of anterior horn cells and focal destruction throughout the brain.

A case of encephalomyelitis following vaccination against yellow fever was described by Lhermitte and Fribourg-Blanc[16] in 1936. This case came to autopsy fifteen

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months after the illness in the nervous system began and so resembled multiple sclerosis clinically and in the pathologic lesions that it strongly suggested to one of us[24] that allergy might be a cause of, or a mechanism in, the production of multiple sclerosis and that allergy might be the common factor underlying the breaking up of myelin in all demyelinating diseases of the nervous system.

In 1936, Kennedy[17] suggested that multiple sclerosis should be studied from the standpoint of allergy. The most interesting case that he reported was that of a physician who was sensitive to pork, suffered from recurring eczema and retrobulbar neuritis with a cerebellar seizure and a slight hemiplegia with homolateral severe thalamic sensations after "inadvertently crossing the pork-line," as the patient himself stated.

In 1938, Pardee[18] reported a case of violent convulsions due to ingestion of chocolate. Clark[22] described cases of convulsions from foods in 1939.

Finley[19] in 1938 wrote a paper of great interest dealing with encephalitis occurring with vaccination, variola and measles. This paper, coupled with the case of encephalomyelitis described by Lhermitte and Fribourg-Blanc,[16] suggested further the idea that "allergy . . . is . . . an important factor in the pathogenesis of encephalitis associated with vaccination, variola, and measles." Ross[20] in 1939 described allergic response to honeybee stings. Baer and Sulzberger[21] in 1939 studied a group of forty cases of multiple sclerosis from the point of view of atopy. Their comment and conclusions in part follow: "In our opinion and experience the incidence of atopic sensitivity found in this group of cases of multiple sclerosis is little higher than that which is to be expected in any equivalent unselected group studied by the same methods." This, of course, has been the experience of most neurologists but such a conclusion, as they themselves admit, adds nothing for or against the hypothesis that some sort of antibody-antigen reaction may be the factor responsible for the initial breakup of myelin in this disease.

Winkelman and Moore[23] in 1941 reviewed the literature on "Allergy and Nervous Diseases" and showed the increasing importance placed on allergy in the etiology of many nervous and mental diseases. They presented cases of migraine, epilepsy and focal lesions of the brain in which the clinical picture has been best explained on an allergic basis. Rich[26] in 1942 discussed the rôle of hypersensitivity in periarteritis nodosa. Scarlatinal encephalomyelitis has been described by Winkelman.[25] One case showed a diffuse inflammation with perivascular necrosis which he interpreted as possibly due to a virus which was dormant in the central nervous system and which was stimulated by the streptococcal infection. Ferraro[28] reported two other cases and interpreted the perivascular inflammation with microglia proliferation and vascular changes as an allergic response.

Hurst[29] in 1944 wrote a comprehensive review of demyelinating diseases of the nervous system but seemed to doubt that a relation exists between allergy or anaphylaxis and demyelination. In summary, he said in part, " . . . The known antecedents of demyelination and the means by which it may be produced experimentally are very diverse, and appear to include no common determinant more narrowly specific than injury to the white matter of one type or other. . . . Demyelination appears to be the response of the white matter to injuries short of those immediately lethal to the tissues." Cooke[30] has recently summarized most of the knowledge pertaining to allergic neuropathies.

Although the numbers involved are small, the development of a "multiple-sclerosis-like" disease in four of seven workers engaged in research on the disease "swayback" in lambs,[60] hitherto regarded generally as due to copper deficiency, is very suggestive that there is some common factor between the two diseases. Whether this factor is a virus, a toxin, a deficiency or an antigen is, of course, not known.

STUDIES ON EXPERIMENTAL ANIMALS

The experimental analysis of allergy in the nervous system may conveniently be divided into two parts: (1) encephalomyelitis produced by vaccination or immunization with nervous tissue and (2) diseases of the nervous system produced by other mechanisms, such as the Arthus phenomenon and passive immunization with anti-brain or Forssman antibodies.

Hurst[34] in 1932 reviewed the literature concerning paralytic accidents occurring in man following anti-rabies therapy and in experimental animals following injections of brain. Numerous experiments had been performed beginning in 1898 using rabbits, rats and dogs which were given injections of aqueous suspensions of ox, rabbit, human and monkey brain and various types of anti-rabies vaccine. Paralyses were relatively infrequent but the best of these experiments provide interesting data, notably the reports by Miyagawa and Ishii,[31] Koritschoner and Schweinburg,[32] Stuart and Krikorian[33] and Hurst.[34] In general, the pathologic picture was inconstant, varying from nothing to explain the paralysis to moderate perivascular inflammation throughout the brain and leptomeninges. Additional changes in neurones, myelin sheaths, axis cylinders and glia were described by Miyagawa and Ishii[31] but the lack of correlation of so many changes prohibits adequate interpretation of their findings. However, concerning the nature of the antigen, it was found that rabies virus or toxin was not necessary but that the active paralyzing agent was present in aqueous suspensions of normal brain.

Although the opinions of various workers analyzing the experimental[33,55] and clinical[48,49] aspects of the problem differed somewhat, it was also found that the antigen probably could be partially destroyed by phenol and heat. Concerning the mode of action of the antigen, it is also of interest to note the following hypotheses: There was an inherent predisposition of the individual to the disease; the injections of brain were not directly toxic but were one of several means of activating some unidentified latent factor or factors.

Rivers and Schwentker[41] extended the experiments of Rivers, Sprunt and Berry[38] by producing paralysis in monkeys more regularly with more prolonged courses of injection and by finding demyelinization on microscopic examination of the central nervous system. Ferraro and Jervis[47] repeated these experiments almost exactly and thus established the disease on more precise neuropathologic grounds. Concerning the antigen, it is to be noted that its nature had been complicated by the addition of an alcoholic extract to the aqueous suspension. Concerning the mode of action of the antigen, only the allergic theory had come into ascendency. Thus, there was a pause important in consolidating the findings into a coherent picture although at the expense of a complicated and prolonged technic.

By no means have all experiments along these lines been successful. Hurst[29] injected suspensions of human brain and alcoholic extracts of rabbit brain into monkeys and suspensions of pig brain into sheep and lambs repeatedly over a period of one year without producing any disease. Innes and Shearer[50] injected suspensions of rabbit brain into sheep and lambs three times a week for one year also without producing any disease.

More recently Morgan,[58] and independently Kabat, Wolf, and Bezer,[59] by using special adjuvants have produced paralyses in monkeys regularly and rapidly following a single or only a few injections. Several antigens have been used, in general the effectiveness paralleling the myelin content, except for peripheral nerves which failed to produce the disease.

There has been much speculation as to what portion of brain is the antigenic material responsible for allergic encephalomeylitis. From the evidence at hand, it is suggested that the following materials extractable from brain are antigenic (really hapten in nature in that they react with specific antibodies but do not stimulate the

production of antibodies unless combined with a suitable adjuvant):

1. Purified but as yet unidentified material soluble in cold alcohol.[37,39,40,44]
2. "Protagon," soluble in hot alcohol but insoluble in cold alcohol;[44] composed of a mixture of sphingomyelin and galactolipins.[45]
3. "Sphingomyelin."[44]
4. "Neurokeratin," soluble in water but insoluble in all common solvents, and present in bacterial cultures on brain-broth.[52]
5. Material present in aqueous suspensions of gray matter but as yet not further identified.[40,44]

There is, unfortunately, no evidence that allergic encephalomyelitis is caused by any of these five fractions, although the "alcohol-soluble hapten," "protagon" and "neurokeratin" are more concentrated in the white than in the gray matter as apparently is the paralytic antigen.

Some experiments on allergy in the nervous system have utilized the Arthus phenomenon in which the injection of antigen into sensitized animals intrathecally produced an acute meningitis,[36,42] or intracerebrally produced a focal hemorrhagic necrosis[35,43,46,55] and disseminated secondary foci of inflammation and demyelinization.[51] Alexander and Campbell[46] examined the local reaction in guinea pigs and observed a large central zone of hemorrhagic necrosis without patent blood vessels. This was infiltrated with neutrophiles, microglia and oligodendroglia and later by astrocytes. It was surrounded by an anemic zone although the blood vessels were patent. They interpreted their findings as demonstrating a primarily vascular hypersensitivity, possibly even primarily endothelial, with secondary thrombosis of vessels. They believed with Gerlach that there was a quantitative difference only between their allergic and control animals; and they disagreed with Rössle, who thought that there were many eosinophiles as well as the quantitative difference. Jervis, Ferraro, Kopeloff and Kopeloff[51] observed not only a local necrosis typical of an Arthus phenomenon but also scattered cellular reactions with giant cells and demyelinization at other points throughout the brain. These, they believed, were indicative of a secondary allergic response, perhaps to the broken-down brain tissue which then became antigenic. These secondary reactions consisted of demyelinization, a perivascular inflammatory reaction with giant cells, hemorrhage, thrombosis and fibrosis of blood vessels, necrosis and gliosis.

A type of passive immunization was used by Hurst and Atkinson[29] who injected sheep or rabbit anti-pig-brain-serum intrathecally into pigs to produce a widespread meningitis, choroiditis and encephalitis but no demyelinization. Hurst[29] injected rabbit or goat anti-monkey-brain-serum intrathecally into monkeys with the same results. Jervis[54] injected Forssman antibodies (rabbit anti-guinea-pig-kidney-serum or anti-sheep-red-blood-cells-serum) into the carotid artery of guinea pigs and observed ataxia and nystagmus. Pathologically, the blood vessels were dilated and congested and there were hemorrhages. There was a diffuse degeneration of neurones and a mild glial reaction; moreover, there were disseminated foci of softening consisting of areas of demyelinization with compound granular corpuscles. There were no giant cells and blood cells were thought to be more rare than in the other types of anaphylactic experiments using brain vaccines. Jervis thought that the Forssman antibody passed through an impaired blood-brain barrier. One would expect guinea pig tissue, including brain (although it apparently has not been tested[57]), to contain Forssman antigen with which the injected antibody might react.

Ferraro[56] discussed the pathology of demyelinating diseases, correlating studies on man and experimental animals, as an allergic reaction of the brain with emphasis on the vascular changes. The vascular reaction consisted of a perivascular exudate which he stated to be always present in acute cases and almost always in chronic cases, which contained lymphocytes and

Gitter cells and other elements, and which itself varied in intensity but was not related to the intensity of the demyelinization. The blood vessels were also thickened and frequently thrombosed and there were areas of necrosis and hemorrhages occasionally in the acute cases. Ferraro believed that the term "reactive allergic inflammation" should be added as a new term to explain this vascular reaction. He thought that it coordinated Putnam's views that the thrombi might be allergic or that there might be an allergic instability of the blood-clotting mechanisms which would also produce a vascular type of lesion. He also stated that giant cells up to now had been underemphasized and that these were sometimes glioblastic tumor nodules such as Scherer described. Ferraro thought that the antigen might be derived from an infectious agent, as either an exo- or endo-toxin, or from products of metabolism and diet; that there might be precipitating factors such as fatigue, hyperventilation, trauma, heat, cold or endocrine disturbances; and that later the antigen might be developed from the gray or white matter of the brain. The difficulties in the past, Ferraro believed, have been (1) a tendency to create new clinical or pathologic diseases easily, (2) a lack of discrimination between the chronic and acute pathologic changes, (3) a tendency to be dogmatic in labelling a disease as inflammatory or degenerative and (4) a lack of experimental support for the establishment of a link between the acute and chronic diseases on the basis of a vascular reaction. Parenthetically, we might add that not only do these objections still remain valid, but other objections are at hand, namely, the assumption that processes which look alike pathologically are otherwise alike and the disregarding of important clinical data in the tendency to lump all the demyelinating diseases together. Ferraro believed that hemorrhages and neutrophiles were seen only in acute cases and that the processes of edema, lymph stasis, necrosis, lymphocytic, histiocytic and giant-cell reactions and repair were fundamental to the disease process. He agreed with Klinge that the time-dose relationship was very important, a large dose producing a typical Arthus phenomenon with a hemorrhagic phlegmonous reaction, whereas smaller repeated doses over a period of weeks produced leukocytic and mononuclear inflammation or repeated over several months produced monocytic and histiocytic and giant-cell reaction without neutrophiles.

By contrast, Hurst,[53] summarizing his experiments on demyelinization produced by cyanide, azide or other chemicals, observed that "nevertheless, demyelination must be mediated by enzymatic processes and must ultimately be explained on a biochemical basis." Later, however, in commenting upon his own experiments with cyanide, Hurst[29] said: "Massive single or repeated doses usually damaged chiefly the cerebral or cerebellar cortex. Repeated (less often single), rather smaller doses led to bilateral necrosis in the basal ganglia, especially the globus pallidus, or in the cerebral white matter or in both. In a remarkable manner, necrosis often developed suddenly or simultaneously over wide tracts of the white matter after a dose of the poison tolerated previously on many occasions." Again, concerning azide, he stated: "Necrosis in the optic connections followed singie or repeated large doses leading to lengthy unconsciousness or developed abruptly from summation of the effects of many small doses each insufficient to evoke marked nervous symptoms. . . . These sudden marked effects could not be explained on the basis of mere accumulation of the poison in the system; it seemed probable that repeated small insults brought the nervous tissues to a state in which a further small dose of the poison, one normally tolerated, produced the most serious consequences." We believe that these statements, especially the last, virtually define the term "hypersensitivity" or "allergy."

SUMMARY

Clinically, allergic manifestations in the nervous system may be produced by the

ingestion of food, inhalation of pollen, injection of serum or vaccination against bacterial or virus diseases or as complications of various diseases. These manifestations include headache, somnolence, convulsions and signs of focal or general central or peripheral nervous system disease. Pathologically, peripheral neuritis, myelitis, meningitis and encephalitis may be found, sometimes with disseminated foci of demyelinization or periarteritis nodosa. Whether classical chronic multiple sclerosis falls into this group is not known.

Experimentally, a meningoencephalomyelitis, sometimes with disseminated foci of demyelinization, can be produced in ways strongly suggestive that allergy is important: by immunization or vaccination with a presumably normal brain, the antigen apparently being concentrated in the white matter of the central nervous system; by the intracerebral injection of antigen into animals immunized against the antigen, a local hemorrhagic necrosis similar to the Arthus phenomenon also occurring and by the injection of Forssman antibodies into the carotid artery of guinea pigs. Although this condition is comparable to acute disseminated encephalomyelitis or acute multiple sclerosis in human beings, there is no evidence that a picture comparable to classical chronic multiple sclerosis has been reproduced experimentally.

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Reviews

Normal and Abnormal Heart in the School Child*

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THE value of periodic physical examinations among school children for the purpose of discovering hitherto unrecognized abnormalities of the heart is now well established. However, every examiner should be cautioned that his zeal for uncovering cardiac disease should be somewhat tempered when he must decide upon the significance of adventitious cardiac sounds or cardiac arrhythmias in children. Too often normal variants are erroneously ascribed to structural alterations in the heart or its great vessels. For this reason the present discussion concerning the recognition of the abnormal heart in the school child will be prefaced by allusions to the criteria by which we recognize the normal heart.

THE NORMAL HEART

Functional Systolic Murmurs. 1. *Originating over the Mitral Area:* The systolic murmur heard at the apex of the heart frequently poses a problem of differential diagnosis between an acquired mitral lesion, a congenital defect and a functional murmur. However, if careful attention is paid to the length, intensity, extent of transmission, direction of transmission, point of maximum intensity, constancy of the murmur, associated presence of a thrill or cardiac enlargement, influence of respiration, postural change and exercise, a correct decision as to its real significance can usually be made. The past history, insofar as it may suggest antecedent rheumatic infection, is of great contributory importance. It should be remembered, however, that about 20 per cent of subjects with unquestionable chronic rheumatic heart disease do not give a history of antecedent rheumatic fever. The quality of the murmur cannot be considered of value in differential diagnosis inasmuch as both functional and organic mitral systolic murmurs can be blowing or harsh. A functional apical murmur, however, never entirely replaces the first heart sound, is rarely loud, is fairly well localized to the mitral area except when it represents a transmitted functional murmur from the pulmonic valve area, is frequently inconstant from day to day or during different cardiac cycles and is considerably modified by postural change, exercise or respiration. In addition, a functional murmur is never associated with a thrill, cardiac enlargement or an apical or basal diastolic murmur.

2. *Originating at the Pulmonic Valve Area:* Functional systolic pulmonic murmurs are extremely common, having been variously estimated to be found in 30 to 60 per cent of healthy children. In contrast to the functional systolic apical murmur, the functional systolic pulmonic murmur is usually harsh and usually replaces the first heart sound. It, too, is never associated with a thrill, cardiac enlargement or a diastolic murmur. It is always accentuated during forced expiration with the child leaning forward. This functional murmur is usually more widely transmitted than the functional apical murmur and, for this reason, can frequently be heard over the apex of the heart and to the right of the sternum. If

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the heart is overactive, a sensation suggesting a thrill may be felt over the site of the pulmonic valve by the palpating hand; with care it easily can be established that the purring quality of a true thrill is lacking. Such a murmur is more frequently encountered in asthenic individuals than in those with other types of body builds. With the aid of the fluoroscope and by comparison between radial and femoral pulses, such functional murmurs can be differentiated from organic, basal systolic murmurs produced by anomalies such as persistent ductus arteriosus or coarctation of the aorta.

3. *Precordial Murmur of Still:* This murmur is similar to the sound produced by the twanging of a tense, low-pitched string of a base violin. The murmur is so low-pitched that it has no blowing quality at all. In fact, its pitch is quite similar to that of the first apical sound itself so that the effect is one of a prolongation of the first sound almost until the second sound is heard, offering difficulty to the examiner in deciding precisely when the first sound really ends. This murmur usually goes unrecognized, probably because of the poor contrast in quality between the first apical sound and the succeeding murmur and because of the relatively few descriptions of it in the literature. The likelihood of its being overlooked is enhanced by the fact that the murmur may be of only moderate intensity, with its point of maximum intensity, usually in the mid-precordium or somewhat below it but sometimes quite near the apex.

Mid-systolic Click. This sound occurs infrequently. It is a definite extracardiac sound but is heard best over the cardiac area, usually being loudest near the apex of the heart. It always appears as though it is very close to the examiner's ear and as though it is immediately beneath the chest piece of the stethoscope. As its name implies, its quality is like that of a click made by the sound device frequently used by elevator starters. It is best heard when the child is leaning forward and usually disappears when the recumbent position is assumed. Its cause is as yet unknown but it is definitely not due to pericardial adhesions or any other type of structural cardiac disease. It is never associated with cardiac enlargement. It is notoriously inconstant, being present at one examination and absent at another time.

Cardio-respiratory Murmurs. In this category are included all murmurs, systolic or diastolic in time, which are obviously related to the dynamics of respiration. Although the majority are systolic in time, some can be heard during the diastolic phase. They usually sound close to the ear and appear only during the inspiratory or expiratory phase of respiration. Their location is variable although most are heard best over the base of the heart either to the right or left of the sternum. Brief periods of hyperventilation usually abolish these murmurs entirely. They are not associated with thrills or cardiac enlargement. They are extremely inconstant, being heard at one examination and absent at other times.

Split Heart Sounds. In this category are included physiologic split first heart sounds and physiologic split second heart sounds. When physiologic splitting occurs, the two components are not widely separated and there is no associated evidence of heart disease such as the presence of diastolic murmurs or cardiac enlargement. In children, a split second pulmonic sound is a common occurrence.

Physiologic Third Heart Sound. This sound may simulate a gallop rhythm and thereby suggest the presence of organic heart disease. However, the differentiation is easy since the physiologic third heart sound, like all other physiologic heart sounds, is unassociated with enlargement of the heart or significant valvular lesions. Actually, a third heart sound is present during each cardiac cycle in all normal individuals but it is usually inaudible except in those with thin chests and active circulations. The physiologic third heart sound is of low pitch and intensity and is best heard by employing the bell type of stethoscope chest piece lightly applied to the chest wall with the subject in the recumbent or left lateral recumbent position. It practically always disappears when the child is standing. It

occurs at the time of rapid ventricular filling. Its only importance lies in the fact that it may be confused with the summation gallop rhythm of first degree A-V heart block and, therefore, may suggest the existence of an active carditis.

Physiologic Arrhythmias. Exaggerated influence of the vagus nerve upon the heart in children is a usual occurrence. For this reason, sinus arrhythmia or sino-auricular heart block are not uncommon in children. These types of disturbances in rhythm have no pathologic significance and can always be abolished by exercising the child since such a maneuver inhibits vagal activity. They are usually most evident when the child is in the recumbent position and are least evident when the child is standing.

We are now prepared to review the physical findings which indicate or suggest the presence of an abnormal heart in school children.

THE ABNORMAL HEART

Thrills. In addition to detecting the position of the apical impulse, palpation of the heart is important in that it provides us with a means for discovering the presence of thrills. It can be considered an accurate rule that a significant thrill cannot be palpated over the precordium unless there is an audible murmur. For this reason, thrills associated with murmurs which are themselves diagnostic are of relatively little importance. Such a thrill is the apical diastolic or presystolic thrill occurring with the diastolic murmur of mitral stenosis. A continuous, often widespread thrill felt with patent ductus arteriosis gives only confirmatory evidence to the continuous murmur. For this reason, the presence or absence of a thrill does not in any way influence the examiner in deciding whether one is dealing with an abnormal heart. It should be mentioned that the vibration of the contracting ventricle, especially in those with thin chests, may suggest the presence of a thrill but the purring quality of a true thrill is lacking under those circumstances. Statistically, thrills are more often encountered in children in association with congenital defects; from this standpoint, it is important to seek for thrills in order to help decide whether one is dealing with a congenital or acquired valvular lesion or defects in one of the septa.

Cardiac Enlargement. Of all physical signs, the presence of cardiac enlargement is undoubtedly the most important in detecting the presence of organic cardiac disease. However, in the child in whom structural changes in the heart have occurred either as a result of congenital anomalies or as a result of acquired rheumatic disease, cardiac enlargement will practically never be encountered without associated murmurs which are easily detected. In the child, cardiac enlargement can be established more easily than in the adult because the apex beat is easily palpable. In this regard, it should be remembered that the apex beat in the normal child is felt frequently in the fourth interspace and, therefore, the demonstration of an apical thrust in the fifth interspace should make one suspicious that cardiac enlargement exists. When any pronounced degree of cardiac enlargement exists, systolic retractions are a common occurrence even in the absence of pericardial or pleuropericardial adhesions. When cardiac enlargement and valvular lesions are detected in a colored child, it is most important to palpate for an enlarged spleen because not infrequently such cardiac findings may be the result of sickle-cell anemia. Extreme degrees of cardiac enlargement such as one sees in the adult are practically never encountered in children unless they are confined to bed with some severe, acute cardiotoxic illness. Rarely is it possible to encounter cardiac enlargement in the child in the absence of associated valvular lesions. This type of hypertrophy is the result of so-called idiopathic hypertrophy or the result of glycogen storage disease.

Organic Systolic Murmurs. 1. *Aortic Systolic Murmur:* A systolic murmur heard over the second interspace to the right of the sternum may be accepted as evidence of aortic valve involvement by a rheumatic process. However, there are two exceptions to this conclusion: First, it must be ascertained that

this murmur is not merely transmitted from the pulmonic area. Second, a very soft and labile systolic aortic murmur may be caused by the emotional tachycardia and hypertension of physical examination or by the presence of a secondary anemia. These possibilities can be tested by repeated examination and by obtaining a blood count. Occasionally, such a murmur is found in association with coarctation of the aorta and this diagnosis can be confirmed by noting a disparity between the blood pressure in the arms and the legs or by noting the absence of a pulse over the femoral arteries. Having decided that a systolic murmur in the aortic area is due to rheumatic involvement of the aortic valve, the diagnosis of aortic stenosis is still not justified. The latter is rare even in rheumatic hearts which have suffered a series of damaging episodes. The criteria for diagnosing this valvular lesion include a harsh aortic systolic murmur transmitted into the vessels of the neck, low pulse pressure, left ventricular hypertrophy, systolic thrill and absent second aortic sound.

2. *Apical Systolic Murmurs:* If a moderately loud or extremely loud systolic murmur is heard at the apex in the course of a routine examination and is of maximal intensity at that point, is of blowing quality and is transmitted towards the axilla, it is probably well to assume that this murmur is an expression of mitral insufficiency due to rheumatic heart disease. The greatest difficulty in interpreting the significance of an apical systolic murmur arises in the case of the incidental finding of a systolic murmur which is maximal at the apex, is of low or moderate intensity, is of blowing quality and is transmitted very little or not at all to the left. Even if there is no antecedent history of rheumatic fever, it is still not possible to say with assurance that the murmur may not be a residual of rheumatic heart disease since 25 per cent of subjects with chronic rheumatic heart disease are unaware of a previous attack of rheumatic infection. Typical migratory polyarthritis, which is the one sign of rheumatic disease sufficiently dramatic to give rise to a satisfactory description by the layman, occurs only in a minority of all cases of rheumatic disease in children. Here again, the presence or absence of associated cardiac enlargement may help one decide as to the true significance of a systolic murmur. However, even when all evidences to support the diagnosis of an organic murmur may be lacking, it is still possible that one might be overlooking an organic lesion. Life insurance statistics show that in a random group of individuals with systolic apical murmurs of all sorts there is a mortality rate of 56 per cent above the expected rate. The diagnosis of an organic mitral lesion cannot, therefore, be made solely on the basis of a systolic murmur confined to the apex. It is recommended that all such persons be seen periodically at intervals varying up to six months according to the circumstances of the case. Physical examinations at each visit should be supplemented by laboratory, x-ray and electrocardiographic examinations at longer intervals.

Diastolic Murmurs. Provided a diastolic cardiorespiratory murmur can be excluded, the presence of a diastolic murmur always indicates that organic heart disease is present. The two most common diastolic murmurs are those produced by mitral stenosis and aortic insufficiency. Each will now be considered separately.

1. *Diastolic Murmur of Mitral Stenosis:* In attempting to elicit this murmur, the examiner should always place the child in the left lateral decubitus position. In the child, the murmur of mitral stenosis usually does not take the form of the classical crescendo presystolic rumble ending in the snap of the first mitral sound; it appears more frequently as a softer sound, mid-diastolic in time and slightly rumbling in quality which ceases before the first sound appears at the apex. In some children, especially in those who have sustained considerable cardiac damage, it may appear in the classical adult form, namely, the presystolic crescendo rumble ending in the snapping first sound. The diastolic murmur of mitral stenosis in the child may or may not be accompanied by an apical systolic

murmur of mitral insufficiency. Associated enlargement of the cardiac chambers may or may not be evident but usually some cardiac enlargement can be detected. An associated thrill will be palpable if the murmur is sufficiently intense.

2. *Diastolic Murmur of Aortic Insufficiency:* The aortic diastolic murmur is also pathognomonic of an organic valvular lesion, namely, aortic insufficiency. Its presence in the child is practically always the result of rheumatic heart disease and, therefore, is usually associated with a mitral valve lesion. However, there are undoubtedly instances when it can exist as an isolated lesion even when due to rheumatic fever. Rarely is it the result of a congenital anomaly of the aortic cusps, in which case the associated stigmata of coarctation of the aorta are usually present. As in the adult, this murmur frequently escapes detection because it often can be heard only with the child bending forward at an acute angle and with the breath held in expiration. Occasionally, it may be audible only when the child is examined in the prone position. In attempting to elicit this murmur, the examiner should always employ a chest piece with a diaphragm or listen with the bare ear against the chest. In children, the diastolic murmur of aortic insufficiency is likely to appear in somewhat different form than it does in adults. It usually has a very hollow sighing quality as compared with the more low-pitched and full-bodied aortic diastolic murmur of adults. Its point of maximum intensity is usually in the third left interspace close to the border of the sternum; and its direction of transmission, when it is sufficiently intense, is in a diagonal line toward the apex. However, even when the examiner hears this transmitted murmur first at the apex, its difference in quality from the somewhat rumbling apical diastolic murmur of mitral stenosis should suffice to indicate its origin. An associated systolic aortic murmur is common.

3. *Diastolic Murmur of Persistent Ductus Arteriosus:* A diastolic murmur produced by persistent ductus arteriosus never occurs without a systolic murmur which is best heard over the pulmonic area. When the diastolic murmur of a persistent ductus arteriosus is present, it lends to the murmur the quality popularly described as "machinery" murmur. Under these circumstances it is practically always associated with a thrill. This is in contrast to the diastolic murmur of aortic insufficiency or the diastolic murmur of mitral stenosis. The diagnosis of persistent ductus arteriosus can also be readily confirmed by a fluoroscopic examination.

Cardiac Arrhythmias. The benign nature of sinus arrhythmia, occasional premature contractions and sino-auricular heart block in children has already been alluded to in an earlier portion of this discussion. However, it should be remembered that occasionally more serious types of arrhythmia may be encountered. For instance, a regular rhythm with a heart rate of 60 or below may indicate the presence of complete A-V heart block. In contrast to a sinus bradycardia, the slow heart rate of complete heart block will not be accelerated by exercise. Also, during some of the cardiac cycles, there usually is a sudden intensification of the first heart sound. In children, complete heart block may be the result of congenital or acquired heart disease. The congenital form is frequently associated with a normal-sized heart and signs of interventricular septal defect but this associated anomaly may be lacking. By contrast, the acquired type of complete heart block is always associated with cardiac enlargement, signs of rheumatic valvular disease, easy fatiguability and dyspnea following exertion. Lesser degrees of A-V heart block can be suspected when there is a sudden cessation of all cardiac sounds for the duration of at least one heart cycle or when one can detect summation gallop rhythm. In this type of gallop rhythm, the extra sound is the result of a superimposition of the vibrations produced by auricular systole upon those which occur during the period of ventricular filling. The presence of any degree of A-V heart block in children should always arouse suspicion as to the existence of an active carditis, usually rheumatic in origin.

Juvenile Electrocardiogram

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ALTHOUGH the cause for the phenomenon is not clearly understood, it is a well known fact that the T waves derived from LIV in children are frequently inverted and opposite in direction to those obtained in adults. Recently, however, an examination of the literature failed to reveal a complete description of the juvenile electrocardiographic pattern. Many of the studies on this subject were performed with earlier technics which differed materially from those now employed and resulted in findings not entirely comparable with those obtained at present.

Master, Dack and Jaffe[8] who studied this problem in 1937, employed seven chest positions beginning at the right sternal border in the fourth or fifth interspace (depending on the age and size of the child) and extending at intervals of 2 cm. to a point 10 cm. to the left of the mid-sternal line. The other electrode was placed on the left leg. With the technic employed the T wave is normally inverted in adults when the exploring electrode is on the left side of the chest. In children they found that the T waves were commonly erect in positions 1, 2 and 3, less frequently in 4 and 5 and generally flat or inverted in 6 and 7. They could find no constant relationship between the degree of axis rotation and the frequency of juvenile configuration of the T waves. The authors ascribed the observed electrocardiographic difference in children to the relative predominance of the right ventricle over the left, as compared to adults and to the comparatively greater A-P diameter of the chest.

At about the same time Messeloff and Pomerantz[9] made a somewhat similar study of LIV in normal children and ambulatory children with heart disease. They placed the right arm electrode in the fourth interspace just to the left of the sternum and the left arm electrode on the back of the chest at the same level. The authors found such marked and unpredictable variations of T_4 that they concluded that there was "no justification for the routine use of LIV for ambulatory children with heart disease."

On the other hand, Levy and Bruenn[5] after observing patients with active rheumatic heart disease suggested that T_4 often gave valuable information about the course of the illness. They noted that during a relapse T_4 frequently became more positive. They also put the left arm electrode in the fourth interspace just to the left of the sternum and the right arm electrode posteriorly. Subsequently they employed the left leg as the indifferent point. Their patients were young adults but in view of the frequency of rheumatic fever in youth their reports stimulated further studies in children.

Robinow, Katz and Bohning[10] made an extensive study of the T_4 problem in healthy and rheumatic children. They also investigated the physical and electrical phenomena responsible for the differences noted in the direction of the T waves derived from the chest leads in children and adults. In the technic employed one electrode was placed in the fourth left interspace just beyond the sternum and the other was located posteriorly medial to the right scapula. The

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authors observed a direct correlation between the degree of axis deviation and the direction of the T wave; 80 per cent of the children with right axis deviation had upright T_4s while of those without right axis shift only 30 per cent demonstrated the same phenomenon. It was thought to indicate that right axis deviation was an important although not the sole factor responsible for the presence of an upright (juvenile) T_4 in normal children. The shape of the chest was considered to be of greater importance. They also noted that T_4 was not as stable in children as in adults and suggested that this might explain the discrepancies observed between changes in T_4 and the clinical course of the patients. In serial tracings of some twenty normal children they observed that with the passage of time T_4 generally altered toward the adult form but sometimes deviated away from it.

The authors concluded that the practical value of Liv in children suffering from rheumatic heart disease was definitely limited. "Single records in individual cases add no valuable information and serial curves supply data which may be suggestive and are only confirmatory to that obtained from the ordinary standard 3 leads."

Dwan and Shapiro[1] who also studied electrocardiograms in children noted, contrary to the findings of the previous authors, that the four lead tracings in children appeared to be constant from day to day. It was their impression that Liv in children was of distinct value.

Rosenblum and Sampson[11] examined the electrocardiograms of fifty children between the ages of one month and sixteen years. Using an earlier technic in which the adult T_4 is normally inverted they found an erect T_4 in 64 per cent of their subjects. Of the remainder, 32 per cent had a diphasic T_4 and 4 per cent had inverted or adult forms.

Heard, Burkley and Schaefer[2] took electrocardiograms of premature infants and found erect T_4s (juvenile forms) in four of five instances.

Recently, a survey was made of 300 healthy, adult negroes and a significant number of these were found to have what appeared to be a persistence of the juvenile pattern.[6] The T wave was found to be inverted (present technic, abnormal as made) in CF_2, CF_3 and CF_4, sometimes CF_5 and once in CF_6. The CRT waves, however, were practically always erect, rarely diphasic and never inverted.

In a subsequent investigation[7] of the electrocardiographic abnormalities found to accompany spontaneous left-sided pneumothorax with mediastinal emphysema, the contour of the T waves derived from the thoracic leads bore a striking resemblance to those seen normally in childhood. The T waves in CF_2, CF_3 and CF_4 were generally inverted. Here, too, however, the T waves from the corresponding CR leads were erect.

In view of the differences noted between the CFT and CRT waves and since previous electrocardiographic surveys of children did not apparently include chest leads made with the several standard indifferent points, a study of fifty normal children was undertaken.

All of the children selected for this study were between the ages of six and eleven. They were picked at random from the classes of a primary school in grades from one to four inclusive. The electrocardiograms were made on a wooden table in a room set aside for the purpose at the school. The leads employed were the normal limb leads, CF_2, CF_3, CF_4 and CF_5, CR_2, CR_3, CR_4 and CR_5 and CL_2, CL_3, CL_4 and CL_5. The machine used throughout the study was a Sanborn cardiette.

RESULTS

The findings are summarized in Tables I, II, III. Table I is concerned solely with the

TABLE I

RESULTS OBTAINED WITH CF LEADS

	All Children		Boys		Girls	
	No.	Per Cent	No.	Per Cent	No.	Per Cent
Purely adult forms	14	28.0	9	33.3	5	21.7
Inverted or diphasic T_{CF_2} only	18	36.0	9	33.3	9	39.1
Inverted or diphasic T_{CF_2} and T_{CF_3} only	12	24.0	6	22.2	6	26.1
Inverted or diphasic T_{CF_2}, T_{CF_3} and T_{CF_4} only	2	4.0	1	3.7	1	4.3
Inverted or diphasic T_{CF_2}, T_{CF_3}, T_{CF_4} and T_{CF_5}	4	8.0	2	7.4	2	8.7
Totals	50	100.0	27	99.9	23	99.9

TABLE II

RESULTS OBTAINED WITH CR LEADS*

	All Children		Boys		Girls	
	No.	Per Cent	No.	Per Cent	No.	Per Cent
Purely adult forms	47	94.0	24	88.8	23	100.0
Inverted or diphasic T_{CR_2} only	3	6.0	3	11.1	0	00.0
Totals	50	100.0	27	99.9	23	100.0

* Actually there was only one inverted T_{CR_2}. The other two were diphasic. None of the CR leads showed any degree of T wave inversion.

TABLE III

RESULTS OBTAINED WITH CL LEADS

	All Children		Boys		Girls	
	No.	Per Cent	No.	Per Cent	No.	Per Cent
Purely adult forms	41	82.0	21	77.7	20	87.0
Inverted or diphasic T_{CL_2} only	5	10.0	4	14.8	1	4.3
Inverted or diphasic T_{CL_2} and T_{CL_3} only	3	6.0	2	7.4	1	4.3
Inverted or diphasic T_{CL_2}, T_{CL_3} and T_{CL_4} only	1	2.0	0	0.0	1	4.3
Inverted or diphasic T_{CL_2}, T_{CL_3}, T_{CL_4} and T_{CL_5}	0	0.0	0	0.0	0	0.0
	0	0.0	0	0.0	0	0.0
Totals	50	100.0	27	99.9	23	99.9

results obtained by the use of the CF leads. There were fourteen purely adult forms in the fifty children examined. In the age group studied no constant relationship could be established between the incidence of adult forms and the age of the subjects. Although most of these forms occurred in children of nine, ten and eleven years of age, a large proportion was found in subjects of six, seven and eight years of age. However, a possibly significant difference in the incidence of adult forms was noted between boys and girls; 33.3 per cent of the former and only 21.7 per cent of the latter demonstrated adult graphs. The remainder of the group showed T wave divergence varying between inverted or diphasic T_{CF_2} to inversion of the T wave in all of the CF leads employed. However, it will be noted that the largest proportion of the children had involvement of T_{CF_2} only while progressively smaller groups showed inversion of the T waves in CF_3, CF_4 and CF_5.

In no case was there inversion of T_{CF_5} or T_{CF_4} without equivalent or greater involvement of T_{CF_3} and T_{CF_2}. It will be seen from the illustrative tracings that the greatest degree of inversion occurred in T_{CF_2} with progressive diminution in T_{CF_3}, T_{CF_4} and T_{CF_5} or with erection of the T wave at any point after CF_2. Occasionally there was an abrupt reversal in the direction of the T wave between two consecutive positions of the exploring electrode as in Figure 1.

When the right arm was selected as the indifferent point, a marked change in the incidence of adult forms was noted. Persistence of any trace of T wave negativity was found in only 6 per cent of the fifty children. This took the form of a slight inversion (1 mm.) of T_{CR_2} in one child and a diphasic T wave in the same lead in two others. All of the T waves of these and the other children in leads CR_3, CR_4 and CR_5 were erect and adult in form.

The tracings resulting with employment of the CL leads were intermediate between those obtained with the CR and the CF leads. Adult graphs were found in 82 per cent of the children and the number of intermediate forms was proportionately smaller. T_{CL_5} was never negative and T_{CL_4} was inverted in only one instance. In no case were juvenile forms found in the CR or CL leads where the CF leads resulted in an adult pattern.

Two children had unimportant degrees of left axis rotation but no significant right axis deviation was encountered. No correlation could be made in the children studied between the degree of axis rotation and the incidence of adult and juvenile forms.

COMMENTS

It would appear from the findings that the most puerile electrocardiogram is that demonstrating T wave inversion in the CF leads from the left sternal border to or beyond the apex and even into the axilla. Contrariwise, the least juvenile or most nearly adult form is that which shows T wave alteration in the CF_2 position only. It is, therefore, probable that erection of the T wave occurs first in CF_6 or CF_5 and as the child grows older progressively involves CF_4, CF_3 and finally CF_2. That this is a steady progress is not, however, definitely known. There is some evidence[10] to indicate that fluctuation of the process may occur in healthy children. This has been observed by the author in several instances.

Of considerable interest and some importance are the results obtained by the use of the CR leads. When the right arm is used as the indifferent electrode, there is little if any apparent difference in the precordial tracings obtained from children as compared to those similarly made on adults. Rarely a diphasic or negative T wave is found normally in adults in the second chest position (CF_2)[4] and this is perhaps slightly more frequent in younger subjects.

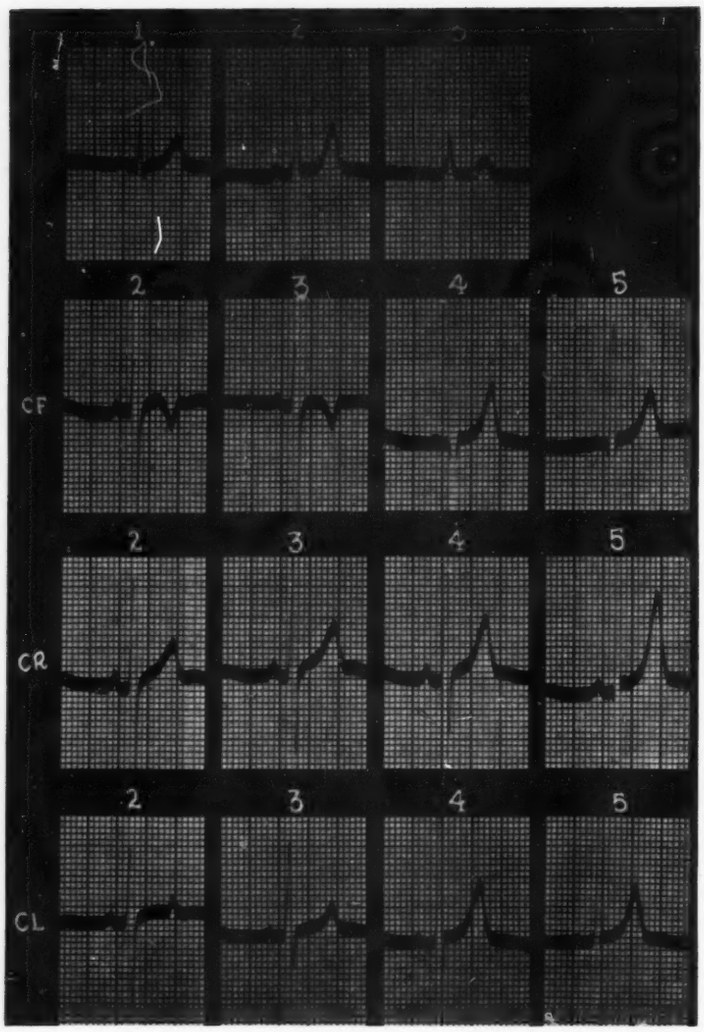

FIG. 1. Characteristic juvenile electrocardiogram demonstrating inverted T_{CF_2} and T_{CF_3} with abrupt erection of T_{CF_4}. T waves in the CR and CL leads are upright.

However, in the more frequently used manner when the exploring electrode was placed just outside the apex no difference at all was found in the CR leads of the fifty children studied. For all purposes, such curves had no earmarks of age and could not be distinguished from an equal number of adult graphs.

Although the study was not repeated, the striking unanimity of direction of the T waves derived from the CR leads in a group as large as this makes it probable that unpredictable variations and fluctuations do not occur. It would appear, therefore, that where the T wave in IVR is of diagnostic value in the adult it would be of similar importance in the child. It should be of particular interest in following the course of such conditions as rheumatic carditis.

The T waves derived from the CL leads were found to be intermediate between CR and CF. They were neither as positive as the first or as negative as the second. Inverted T waves occurred with sufficient frequency in the CL leads to render them of little diagnostic value.

In considering the causes for the differences noted between juvenile and adult T_4s Robinow, Katz and Bohning[10] postulated that the shape of the chest and its physical

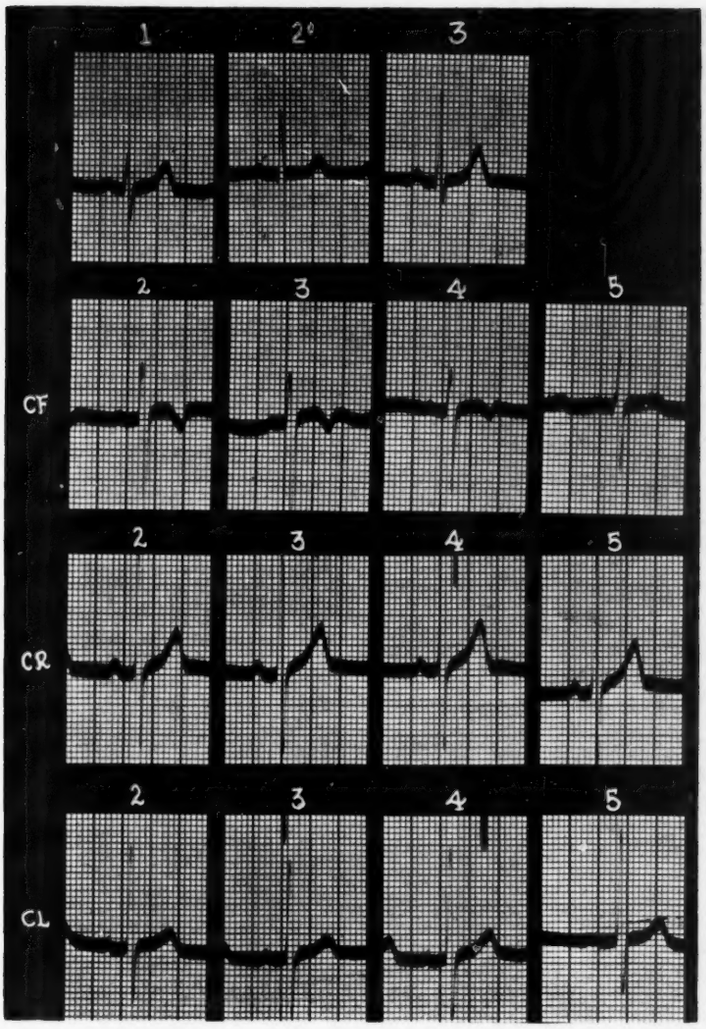

FIG. 2. Characteristic juvenile electrocardiogram with inversion of T_{CF_2}, T_{CF_3} and T_{CF_4}. The T waves in the CR and CL leads are upright.

relation to the heart was of paramount importance. Their work indicated that the amount and character of the tissues interposed between the heart and the chest wall profoundly influenced the character of the electrocardiogram. These features were thought to be sufficiently different in the chests of adults and children to account for the electrocardiographic variations encountered.

In support of this contention are the findings recently observed in two patients with spontaneous left-sided pneumothorax with mediastinal emphysema.[7] The T waves derived from the CF leads in these patients showed various degrees of inversion when the patients were in the supine position and the extrapulmonary air was trapped anteriorly. However, when they were erect and the pneumothorax had shifted cephalad the T waves became erect. Although the mediastinal emphysema was in part responsible, apparently in these patients the physical presence of air between the heart and the exploring electrode interfered with the normal surface distribution of the electrocardiac manifestations and resulted in an altered pattern. In spite of this, however, the T waves derived from the CR leads were relatively unchanged. They were somewhat

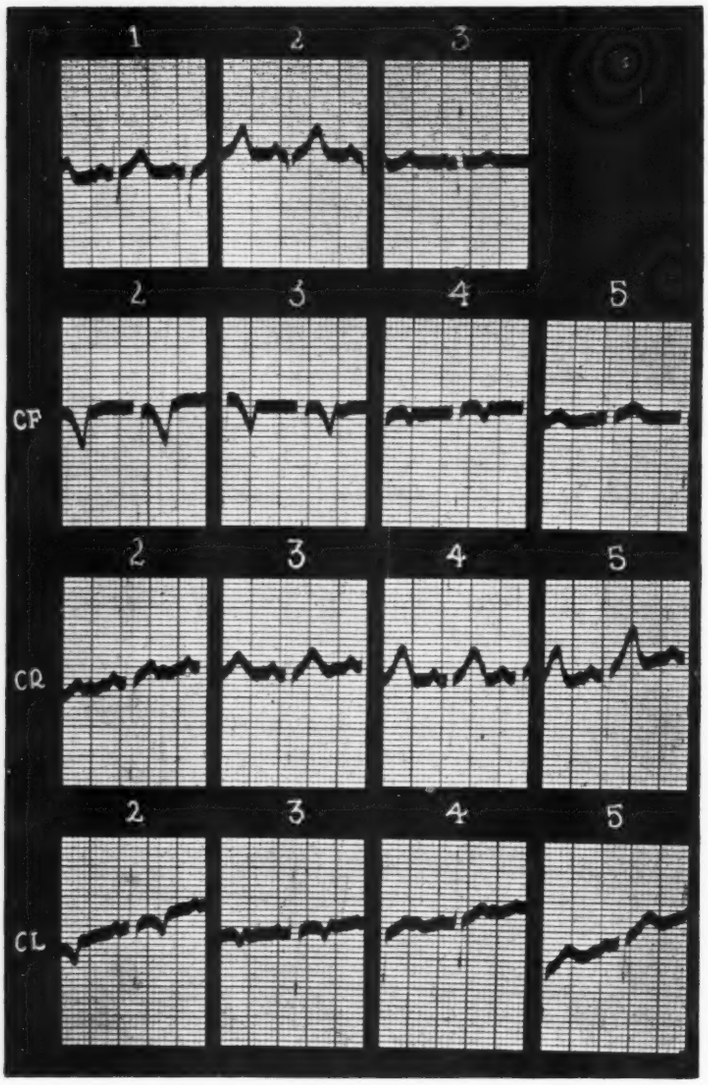

FIG. 3. Characteristic juvenile electrocardiogram. T_{CF_2}, T_{CF_3} and T_{CF_4} are inverted. T_{CL_2} and T_{CL_3} are inverted. The T waves in the CR leads are upright.

lower when made in the supine position but were essentially within normal limits. The cause for this is obscure but it appears likely that the electrocardiographic pattern derived from the CR leads is interfered with to a lesser and relatively inconsequential degree by changes in the extracardiac tissues. In a similar manner it is suggested that differences between adult and juvenile chests are of lesser electrocardiographic importance in the CR than in the CF leads.

This, however, should not lessen the value of the CR leads for the diagnosis of purely cardiac involvement. It is felt that the routine use of IVR in children will be of value and will serve to replace the unpredictable variations and diagnostic inadequacies of lead IVF.

SUMMARY

1. Multiple lead electrocardiograms were made of fifty school children between the ages of six and eleven, in order to determine the normal juvenile electrocardiographic pattern.

2. In the group studied purely adult

forms were more frequently encountered in boys than in girls.

3. Those individuals demonstrating the most juvenile forms had T wave inversions in CF_5, CF_4, CF_3 and CF_2. Those with the most nearly adult forms had negative or diphasic T waves in CF_2 only.

4. It is suggested that change from the puerile to the adult form takes place first in the axillary location and then proceeds medially to the left border of the sternum.

5. The T waves derived from the CR leads of children were not found to be materially different from those of adults.

6. The T waves from the CL leads were intermediate between CR and CF and had no diagnostic advantages over either.

7. No significant relationship could be established between the degree of axis rotation and the incidence of T wave negativity.

8. It is recommended that lead IVR be made routinely in children, in place of IVF which is unpredictable and of little diagnostic value.

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Seminar on Thromboembolism

Dicumarol*

Its Action, Clinical Use and Effectiveness as an Anticoagulant Drug

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THE isolation and synthesis of the compound 3,3′-methylenebis (4-hydroxycoumarin), now generally known as "dicumarol," was reported in 1941 by Link and his associates at the University of Wisconsin.[1,2] Since that time considerable experience has been accumulated concerning the usefulness of this compound in the prevention of intravascular thrombosis in human beings.

The principal physiologic effect of dicumarol on human beings is the marked inhibition of prothrombin activity as indicated by prolongation of the prothrombin time.[3,4] This effect is the same as Link and his associates observed in studies on animals. It is generally assumed, although not conclusively proved, that the primary action of dicumarol is a peculiarly selective inhibition of the formation of prothrombin by the liver. This inhibition is temporary and other functions of the liver are apparently not affected even after long continued use of dicumarol. There is evidence that dicumarol has other inhibitory effects on the coagulation mechanism. Spooner and Meyer,[5] and Wright[6] have shown that it inhibits adhesiveness of blood platelets and Hurn and her co-workers[7] have shown that it increases the antithrombic activity of blood serum. It has been shown that when the prothrombin time is greatly prolonged by dicumarol the coagulation time of whole blood is also prolonged; however, when there is only moderate prolongation of the prothrombin time, the coagulation time of whole blood in glass tubes may not be greatly affected[4] and cannot be correlated with the prothrombin time. Margulies[8] has shown that the coagulation time of venous blood drawn into a silicone coated syringe and tested in a silicone coated glass tube at 37°C., is significantly prolonged after dicumarol has been given even when there is only moderate prolongation of the prothrombin time. Dicumarol prolongs clot retraction time. At first we thought that it frequently increased the sedimentation rate of the erythrocytes but subsequent studies have shown that it probably has little if any effect on the sedimentation rate. It has not been shown that dicumarol has any other physiologic effects on the human body except those exerted on the clotting factors of the blood. We have observed four patients in whom minor allergic reactions, urticaria and headache, developed after dicumarol had been administered.

At present, we believe that the only satisfactory and practical method for measuring the effect produced by dicumarol is the Quick prothrombin time test. Other methods for determining the anticoagulant effect of this drug are either difficult, inaccurate or have not been used sufficiently to prove their value. There is some dis-

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agreement as to whether the test is best done on undiluted plasma or diluted plasma. Shapiro and Sherwin[9] favored the use of a 12.5 per cent solution of plasma in a 0.9 per cent solution of sodium chloride. We still use only undiluted plasma because we believe that the end points are more definite and consistent when undiluted plasma is used.

Dicumarol is effective when administered orally. This is a relative advantage from the standpoint of simplicity of administration. No satisfactory preparation for parenteral administration has been developed. This is a disadvantage from the standpoint of accuracy of dosage. The effect of dicumarol is delayed for twelve to seventy-two hours or longer after a dose has been given. This is a distinct disadvantage when a rapid anticoagulant effect is desired. The effect of dicumarol may persist for seventy-two hours or longer once it has developed. This may be an advantage in maintaining the anticoagulant effect but is a disadvantage when it is desirable to stop the anticoagulant effect rapidly, for example, in case of bleeding.

Early in our experience with dicumarol, it was found that prolongation of prothrombin time varied greatly among different patients after the administration of a certain amount of dicumarol and that the degree of response was usually unpredictable. Hepatic insufficiency, renal insufficiency and dietary insufficiency were found to augment the effect greatly. Some diseases of the gastrointestinal tract, recent operations on the stomach or the intestine and repeated vomiting may greatly decrease or nullify the effect. In patients in whom thrombosis occurred recently they are frequently but not always more resistant to dicumarol; however, there undoubtedly are other factors which may produce relative sensitivity or resistance to the drug which are entirely unpredictable and which unfortunately may vary somewhat from time to time in the same patient. For these reasons the production and maintenance of a certain degree of prothrombin deficiency by dicumarol becomes an individual problem in each case. The amount of dicumarol administered on each day may be arbitrarily fixed but the days on which the drug is given have to be selected on the basis of daily prothrombin time tests. We have believed that it is simpler and just as satisfactory to give one daily dose as it is to give the same amount in divided doses. If daily prothrombin time tests are not done, it is always uncertain whether the doses of dicumarol are producing the desired effect, an inadequate effect or an excessive and possibly dangerous effect.

Because of the importance of the Quick prothrombin time test as a guide to effective and safe administration of dicumarol, it is necessary to emphasize some of the technical features of this test which apparently are not generally appreciated. The exact mechanics of performing the test are simple[10] but the variable in the test is the potency of the thromboplastin. It is useless to state that the normal prothrombin time, as indicated by this test, is a certain number of seconds and it is equally useless to state that a certain degree of prothrombin deficiency, for example 20 per cent prothrombin, is indicated by a certain number of seconds, because the times for these concentrations of prothrombin are entirely dependent on the particular thromboplastin which is used and the way in which it is prepared.[11] Thromboplastins from the same source prepared in the same way also may vary in potency. For these reasons it is necessary at all times for the laboratory worker to know the percentages of prothrombin indicated by prothrombin times of any number of seconds. It is also advisable that the laboratory worker report the prothrombin time to the clinician in terms of per cent of

the normal concentration of prothrombin rather than in seconds. If clinicians become accustomed to discussing concentrations of prothrombin in terms of percentages rather than time, it is possible to compare the results of the tests performed in many institutions or by individual physicians in different laboratories. If seconds are used no such comparison is possible. Some misunderstandings have arisen in the computations of prothrombin percentages from prothrombin times in seconds. There is no way that percentages of prothrombin can be computed accurately by any linear relationship between an elevated prothrombin time and a normal prothrombin time. The only accurate way to compute prothrombin percentages from prothrombin time is to compare frequently the values obtained for prothrombin deficient plasma with values obtained with the same thromboplastin for serial dilutions of two or three samples of normal plasma. Dilutions are theoretically best made with prothrombin-free plasma but actually the same results may be obtained by diluting with an 0.9 per cent solution of sodium chloride. For example, the prothrombin time of normal plasma and of 10, 20 and 30 per cent solutions of normal plasma in 0.9 per cent solution of sodium chloride are obtained with the particular thromboplastin in use. A comparison of the prothrombin time of the plasma of the patient receiving dicumarol with the prothrombin times for these diluted samples of normal plasma will permit a reasonably accurate report in terms of percentage of normal prothrombin. It is worthy of note that the relatively great decrease of prothrombin from 100 to 50 per cent of normal is indicated by only a slight increase in the prothrombin time while the relatively slight decrease in the concentration of prothrombin from 10 per cent of normal to 5 per cent of normal is indicated by a relatively great increase in the prothrombin time.

Our experience has led us to believe that when dicumarol is used as an anticoagulant it is advisable to keep the concentration of prothrombin between 10 and 30 per cent of normal as calculated by the previously mentioned method, because we have encountered thrombosis in some patients in whom the concentration of prothrombin was greater than 30 per cent and most of the instances of major bleeding have occurred when the concentration of prothrombin was less than 10 per cent of normal. When the concentration of prothrombin was kept between 10 and 30 per cent of normal few instances of major bleeding and almost no instances of thrombosis have occurred. This zone of effectiveness and relative safety is a comparatively narrow one and some observers have been satisfied with less drastic reduction in the concentration of prothrombin. This may be sufficient to prevent thrombosis in some patients but is certainly less effective if the stimulus to thrombus formation is strong. We believe that if dicumarol is used at all, a strong attempt should be made to secure the optimal effect in each patient.

The plan of dosage which we have continued to employ since our early experiences with the drug is quite simple. The entire amount for one day is given in a single dose: 300 mg. of dicumarol are given on the first day and 200 mg. are given on each subsequent day that the concentration of prothrombin is greater than 20 per cent of normal. On days when the concentration of prothrombin is less than 20 per cent of normal no dicumarol is given. Even with this method the variability of response among different patients is considerable. In the majority of patients it is quite easy to maintain the concentration of prothrombin between 10 and 30 per cent of normal but in some patients who are sensitive the concentration of prothrombin may quickly drop below 10 per cent of normal. In these

patients we usually cut the dose from 200 to 100 mg. In an occasional patient who is very resistant we increase the dose from 200 to 300 mg.

It has been shown that in most patients large doses of menadione bisulfite (synthetic vitamin K) given intravenously, usually within a few hours will increase prothrombin percentages which have been lowered excessively by dicumarol.[12] This is particularly true in patients who are found to be hypersensitive to the drug when it is employed in the usual doses as indicated previously. If the concentration of prothrombin drops below 10 per cent of normal and remains there for two successive days, 30 mg. of menadione bisulfite may be given intravenously and this usually will raise the concentration of prothrombin above 10 per cent.

We have given dicumarol to hospital patients for periods as long as nine months and have maintained an optimal effect on the basis of daily prothrombin time tests. In a few patients who were not in the hospital, attempts were made to continue dicumarol therapy for even longer periods with less frequent checks of the concentration of prothrombin and to regulate the dosage on the basis of a pattern which has been found effective for the individual patient after a few weeks of carefully controlled therapy. We do not recommend this inadequately controlled therapy since we believe that it cannot be considered either persistently effective or safe.

The use of dicumarol with concurrent heparinization for the first few days is the best method for rapidly instituting and maintaining anticoagulant therapy. Since heparin acts rapidly, it is used to secure an anticoagulant effect during the period after administration of dicumarol has begun and before an adequate effect of the dicumarol has developed. During this period it is usually sufficient to give 50 mg. of heparin intravenously every four hours until the concentration of prothrombin is less than 20 per cent of normal as a result of the effect of dicumarol. Blood for the prothrombin time tests should be withdrawn at least three and a half hours after a dose of heparin has been given as heparin also increases the prothrombin time.[13]

In previous publications we have listed certain contraindications to administration of dicumarol; namely, hepatic insufficiency, renal insufficiency, purpura of any type, blood dyscrasias with bleeding tendency, particularly thrombocytopenia, and subacute bacterial endocarditis. We have believed that the use of any anticoagulant is contraindicated after recent operations on the brain or spinal cord, not because the danger of bleeding is greater but because the consequence of even a minor degree of bleeding at the operative site is great.

Extra caution and an appreciation of increased risk of bleeding are advisable when dicumarol is administered to patients who have open ulcers, granulating wounds or drainage tubes. Nutritional deficiency may increase sensitivity to dicumarol.

The risk of bleeding during administration of dicumarol is small if the plan of dosage described previously is followed and if the contraindications and cautions are observed. Minor bleeding, such as transient epistaxis, local ecchymoses in the skin, small hematomas in operative wounds and microscopic hematuria can be disregarded. Serious and prolonged bleeding has been noted from operative wounds, ulcerating lesions of the gastrointestinal tract and from the urinary tract. It has been encountered by us postoperatively in only 1 per cent of patients who have had thrombosis and in only 2.5 per cent of those who have not had thrombosis prior to administration of dicumarol. We have encountered serious bleeding in 1.4 per cent of non-surgical patients. We have seen widespread hemor-

rhage and ecchymosis in only one patient, a patient with subacute bacterial endocarditis and renal insufficiency, two conditions which are now considered contraindications to the use of dicumarol. The patient died as the result of hemorrhage. We have seen three patients who have died as the result of bleeding from the gastrointestinal tract after they had received dicumarol. One of the patients died before much prothrombin deficiency had developed and the other died after the prothrombin time had returned to normal and had remained normal for several days; therefore, it is unlikely that dicumarol was a factor in the production of the fatal hemorrhage in either patient. The third patient had an inoperable carcinoma of the stomach and the hemorrhage occurred during moderately severe prothrombin deficiency produced by dicumarol.

If serious bleeding occurs it is our practice to give 60 mg. of menadione bisulfite intravenously each day until bleeding stops. Usually it stops within twelve hours after the first injection. We also transfuse 500 cc. of freshly citrated blood if much blood has been lost and repeat this as frequently as necessary. The transfusion of blood is done largely to replace blood. It supplies some prothrombin also but the effect of this usually is transitory.

The purpose of giving dicumarol is to prevent thrombosis. As far as is known it has no effect on a thrombus that has already occurred or an embolus that has already lodged in an artery. Thus the use of dicumarol is always prophylactic and not curative. It is given to patients who are known to have or have had thrombosis, in order to prevent extension of thrombosis or thrombosis in other vessels. Naturally it is not certain that further thrombosis will develop if the patient is not treated. The rationale for the use of dicumarol, therefore, depends to some extent on the percentage chance of thrombosis developing within the period during which dicumarol can be given with adequate supervision. In some situations the percentage chance of further thrombosis or embolism is fairly well indicated by statistical studies of large numbers of cases.

The rationale for the use of dicumarol for the prevention of pulmonary embolism in a patient with venous thrombosis or thrombophlebitis is based on the concept that only a freshly formed thrombus will become detached and form an embolus. If the thrombus remains in the vein for more than a few hours it rarely if ever becomes detached. Thus, in a patient with clinically recognizable venous thrombosis or thrombophlebitis, if extension of thrombosis or fresh thrombosis in other veins can be prevented, embolism can be prevented. Actually, in a large series of patients with postoperative thrombophlebitis who have been given dicumarol, fatal embolism has not occurred although the expected incidence of fatal embolism among such patients is approximately 6 per cent. This strengthens the concept that an embolus only develops from a newly formed thrombus, since the only effect of the dicumarol in such patients is the prevention of fresh thrombosis.

Our greatest experience with dicumarol has been in the prevention and treatment of postoperative thromboembolic disease and this has been the subject of several reports.[4,14,15,16] To date we have supervised the postoperative administration of dicumarol to 1,983 patients; 352 of these patients were given dicumarol because of clinically evident thrombophlebitis and 329 because of pulmonary embolism or pulmonary infarction. As compared with a large series of similar cases in which anticoagulants had not been given, the incidence of subsequent thromboembolic episodes was reduced from 43.8 to 1.0 per cent and the incidence of fatal embolism was reduced from 18.3 to 0.3 per cent among the patients with

embolism; the incidence of subsequent thrombotic episodes was reduced from 25.3 to 2.8 per cent and that of fatal embolism was reduced from 5.7 per cent to zero among patients who had thrombophlebitis. Preliminary heparinization was employed in some patients in both groups. In addition, we have given dicumarol postoperatively to more than 1,302 patients for prophylaxis against thrombosis and embolism. Of these patients, 143 had had thrombosis or embolism at some time prior to the immediate operation. No pulmonary embolism developed in any of these 1,302 patients and thrombosis developed in only two. This was localized to small veins in both subjects. After operation we have continued the administration of dicumarol until the patients have been ambulatory for several days and until they left the hospital; the period of administration usually lasted seven to twenty days. Patients were not kept in bed or in the hospital longer than usual because they were receiving dicumarol.

Dicumarol has been administered successfully to patients with postpartum thrombophlebitis and pulmonary embolism for the purpose of preventing subsequent thromboembolic episodes.[17] Our experience with the administration of dicumarol for this purpose has been limited to nineteen cases (four patients with pulmonary embolism and fifteen with thrombophlebitis). In none of these patients did further thrombosis or embolism develop and in none was there abnormal bleeding or increase in the lochia. Treatment was begun as early as the fifth postpartum day. Two mothers were nursing their babies, and repeated studies of the prothrombin time of the infants showed values which were normal even though the concentration of prothrombin among the mothers was between 10 and 30 per cent of normal. Experimental studies have shown that when relatively large doses of dicumarol are given to lactating rats the nursing baby rats may bleed and die;[18] however, the doses of dicumarol given to the mother rats were relatively much greater than the doses which are given to human beings, in fact, they were sufficient to produce generalized bleeding and death in the mother rats as well. This situation cannot be compared to the controlled administration of therapeutic doses of dicumarol to human beings.

We have given dicumarol to 182 patients with thromboembolic disease which occurred as a complication of trauma, infectious diseases, congestive heart failure, carcinoma, blood dyscrasias or varicose veins or which was of the idiopathic type. Of these patients, 138 had acute thrombophlebitis and forty-four recently had had pulmonary embolism. During treatment with dicumarol fatal embolism did not develop. Non-fatal embolism developed in three patients and subsequent venous thrombosis occurred in four patients. This series of cases is rather small and we have no statistical data to indicate the expected incidence of thrombosis and embolism during the period of treatment if anticoagulants had not been given; however, it is our impression that the incidence was markedly reduced by dicumarol. In several of the patients there had been repeated thromboembolic episodes before dicumarol was given but these ceased after dicumarol was administered. It is not possible to state how long dicumarol should be given to such patients, particularly in those patients in whom thrombophlebitis or embolism complicates congestive heart failure or carcinoma or in patients with recurrent idiopathic thrombophlebitis. It is recognized that in these patients a tendency to thrombosis may exist for a long time, during which it is unpractical to give dicumarol continuously.

We have given dicumarol to seventy-six patients with chronic occlusive arterial disease of the extremities, in some instances

for periods as long as four to six months. In forty patients the disease (thromboangiitis obliterans or arteriosclerosis obliterans) was considered to be in the active phase when dicumarol was given. In thirty-six patients it was given for prophylaxis after amputation. In none of these patients was there any evidence of recurrence or extension of arterial or venous thrombosis during the period in which dicumarol was given. We do not believe that it is practical to give dicumarol to patients with chronic occlusive arterial disease of the extremities unless the disease is in an active phase or unless amputation is necessary.

In patients with acute arterial occlusion of the extremities, either by arterial embolism or thrombosis *in situ*, we have used dicumarol, always with preliminary heparinization, for the purpose of preventing further intracardiac and peripheral arterial thrombosis.[19] It has been our experience that secondary and distally propagating thrombosis from the site of the occlusion frequently occurs in these patients after the arterial spasm has relaxed and that this secondary thrombosis is often the factor which precipitates gangrene. To prevent this secondary thrombosis it is necessary that anticoagulant therapy be started as early as possible and certainly within twenty-four hours after the arterial occlusion has taken place. We have treated eleven patients with arterial embolism and sixteen patients with acute arterial thrombosis *in situ* with heparin and dicumarol. In all of these subjects the diagnosis was made early and the administration of the anticoagulants was started within twenty-four hours after the occurrence of the embolism or thrombosis. There was survival of the extremity in ten of the eleven patients with arterial embolism and in thirteen of the sixteen patients with acute arterial thrombosis. We believe that anticoagulants plus procedures to eliminate arterial spasm and avoidance of thermal trauma to the affected limb are important in the emergency treatment of acute arterial occlusion of the extremities.

There have been four reports of the treatment of acute myocardial infarction with dicumarol. The rationale has been to prevent further episodes of coronary thrombosis during the period of healing of the infarction and to prevent intracardiac thrombosis, venous thrombosis, pulmonary embolism and thrombosis in peripheral and cerebral arteries, all of which have been known to be relatively frequent complications of acute myocardial infarction. Nichol and Page[20] reported the treatment of forty-four patients who had a total of fifty instances of myocardial infarction. These authors expressed the opinion that the incidence of secondary thromboembolic complications was significantly reduced. Peters, Guyther and Brambel[21] compared the results obtained in fifty cases of acute myocardial infarction in which the patients were treated with dicumarol with the results obtained in sixty similar cases in which dicumarol was not administered. They found that the dicumarol apparently reduced the mortality rate from 20 to 4 per cent and that the incidence of pulmonary embolism was reduced from 16.6 to 2 per cent. Wright[22] administered dicumarol to seventy-six patients with myocardial infarction. In thirty-three of these patients the disease was uncomplicated but in forty-three of the patients the drug was given after repeated episodes of coronary occlusion or thromboembolism had occurred. Four patients in the first group and eleven patients in the second group died. The author believed that this represented a reduction in mortality for the types of patients treated. In a recent article, Parker and Barker[23] compared the results obtained in fifty cases of acute myocardial infarction in whom dicumarol was administered with the results

obtained in one hundred similar cases in which this drug was not administered and which previously had been reported by Nay and Barnes.[24] Secondary thromboembolic complications occurred in 4 per cent of the patients to whom dicumarol was administered and in 37 per cent of the patients to whom this drug was not administered. The mortality rate was 10 per cent in the cases in which dicumarol was administered and 13 per cent in the other group of cases.

In each of these four reports on the treatment of acute myocardial infarction, the series of cases in which dicumarol was administered is too small to permit conclusions as to the value of this drug; however, when considered in the aggregate they appear to indicate that such treatment is of value in preventing secondary thromboembolic complications and probably in the prevention of further myocardial infarction. Further observations on larger series of cases from several institutions will probably be available in the near future.

If anticoagulants are to be used in the treatment of acute myocardial infarction, it would appear that the administration of dicumarol and preliminary heparinization should be started as soon as the diagnosis is made and that the administration of dicumarol should be continued for at least four weeks.

SUMMARY

Dicumarol is a potent and valuable anticoagulant drug. When used properly it appears to prevent intravascular thrombosis in almost all patients. There is considerable and unpredictable variation in sensitivity to dicumarol among different patients. Dosage of dicumarol must be guided by the effect produced in each patient as indicated by the degree and duration of prothrombin deficiency which develops and is indicated by determinations of the concentration of prothrombin in the blood. It is unwise to use dicumarol unless adequate facilities for determining the prothrombin time are available. If the prothrombin is kept between 10 and 30 per cent of normal by administration of dicumarol, thrombosis will almost certainly be prevented and serious bleeding is very unlikely to occur. The action of dicumarol is delayed. When a rapid anticoagulant effect is desired concurrent heparinization is necessary for the first few days. We have found that dicumarol has prevented fatal pulmonary embolism and recurrence or extension of venous thrombosis in patients who have had postoperative nonfatal pulmonary embolism or thrombophlebitis. There is some incomplete evidence to the effect that it will prevent peripheral thrombosis, pulmonary embolism and further coronary thrombosis in patients who have had acute myocardial infarction. Dicumarol with preliminary heparinization is valuable in the treatment of acute arterial occlusion of the extremities. It has also been used safely in patients in whom thrombophlebitis and pulmonary embolism complicated the puerperium and various diseases, in patients with idiopathic recurrent thrombophlebitis and in those with chronic occlusive arterial disease. While statistical confirmation is lacking, it is our impression that in many of these patients thrombosis and embolism have been prevented by administration of dicumarol.

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Case Reports

Dissecting Aortic Aneurysm*

An Unusual Case Having a Previous Healed Dissection and Later Slow Dissection of All Major Aortic Branches

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EVER since Shennan's able monograph in 1934, dissecting aortic aneurysm has received increased attention as evidenced by the number of reports appearing in the literature. It is the purpose of this paper to report an additional case followed both before and after the accident in some detail, which was remarkable because there was a healed dissection, and because the pathological course could be traced clinically from beginning to exitus along the entire aorta and its branches.

Although dissecting aortic aneurysm has been recognized by the pathologists for over two hundred years, the first description having been made in 1728, it was not recognized clinically until 1856. Between that first recognition and 1933, only five correct ante-mortem diagnoses were reported, but in the last ten years it has been described some fifty times. The symptomatology is now sufficiently well defined so that it should usually be diagnosed before death.

PATHOGENESIS

Dissecting aneurysm is a lesion produced by penetration of the circulating blood into the substance of the wall of a vessel with subsequent extension of the effused blood for varying distances between its coats. The sac communicates with the original lumen through a rupture or ruptures of the inner layers of the wall and then usually breaks through either to the exterior or back into the lumen. The primary rupture is usually transverse to the long axis of the vessel while the second tear is along the longitudinal axis. It occurs more often in males with a ratio of two to one, and usually in the fifth to seventh decades. Hypertension is almost always present; syphilis of the aorta is rarely present, and if present is associated with the atherosclerosis responsible for the dissecting aneurysm.

The primary rupture most often occurs in the arch of the aorta in the region of the ductus arteriosus and the right pulmonic artery and is, as stated, transverse. The secondary rupture is usually central to this near the reflexion of the pericardium, and more often into the pericardium than elsewhere, but may be at any level. The dissected space may therefore extend centrally into the coronary arteries or distally to the termination of the iliac arteries. Any vessel arising from the aorta may be dissected and its branches involved.

It is generally conceded that the cause of the primary rupture is the diastolic thrust where the blood comes back against the suddenly closed aortic cusps, especially where the heart is heavy and supported in part by the aorta. This is especially true when the aorta has been stretched by a short, strong ductus arteriosus or compressed by the right pulmonic artery as it passes

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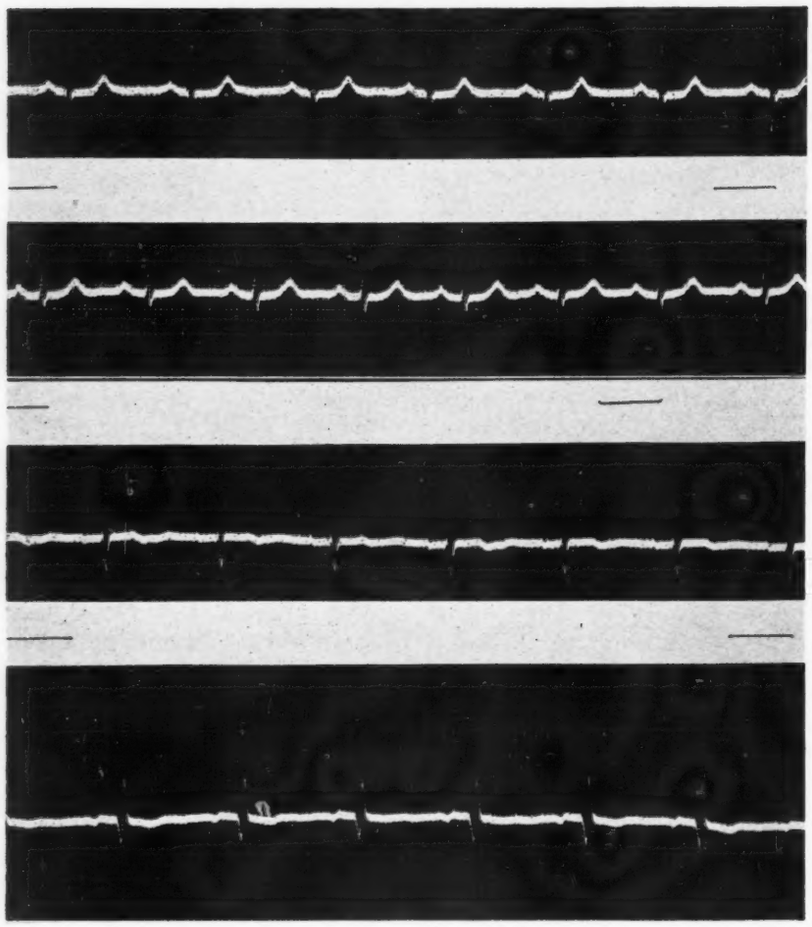

FIG. 1. Electrocardiogram taken at time of original small dissection misdiagnosed as coronary occlusion.

under the arch. However, ruptures do not usually occur through atheromatous plaques but at their edges or through an apparently intact intima. It is therefore believed that degenerative changes in the media which extend into the intima predispose to this condition. And especially does this medial degeneration predispose to dissection between strong inner and outer coats rather than to rupture directly through the whole aorta at once. The pathogenesis includes many factors, mainly: (1) A rise in blood pressure following external or internal trauma; (2) primary rupture through the intima; (3) dissection between the coats and (4) rupture of the sac to the exterior or reentrance into the original lumen.

By external trauma is meant any sudden jarring; by internal trauma any unusual and especially sudden exertion.

SYMPTOMS

Symptoms of Primary Dissection. It is characterized by a sudden onset without premonitory symptoms in a patient otherwise in good health except for hypertension. There is a feeling of something going wrong, often not clearly defined, and usually in the thorax.

Pain is almost invariable and maybe in the thorax, abdomen or both, and very often in the back. This may be extremely severe. Characteristically, the pain usually travels downward from its point of onset, taking from a few minutes to several days. Collapse often occurs. Other symptoms de-

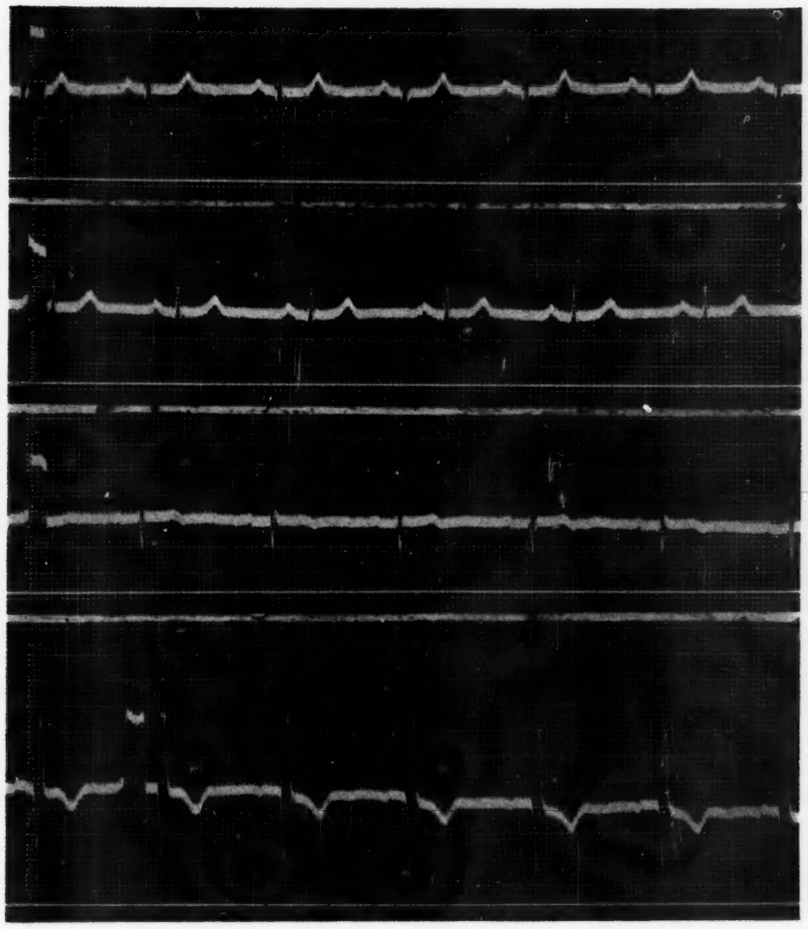

FIG. 2. Electrocardiogram at time of second dissection. Note change in T_3 and T_4.

pend on the rapidity of dissection and the vessels involved. These include choking or strangling sensations in the chest, cyanosis or swelling of the face and neck, dyspnea or orthopnea, dysphagia, pain in the abdomen, kidney regions or legs, and in our case, uncontrollable hiccough and jaundice. The pulse and blood pressure are usually unchanged. There may be slight fever, and leucocytosis is often present. There is usually no change in the electrocardiogram unless dissection extends to the coronary arteries. There is often characteristic widening of the entire aortic shadow to left and right.

DIFFERENTIAL DIAGNOSIS

In the absence of correct diagnosis of dissecting aneurysm various other diagnoses are often entertained and vary with the rapidity and extent of the dissection. These include, coronary or mesenteric obstruction, pulmonary embolism, rupture of the heart, gastric crisis, renal or pancreatic colic, or perforated abdominal viscus.

The course of the disease is variable, but unless re-entrance into the original lumen occurs, practically always results fatally. Exitus may occur from a minute to several months after the original tear, and death is almost always by perforation and without warning. Terminal perforation occurs most often into the pericardium, and then into the left lung or pleura, the free mediastinum or the abdomen.

There is no treatment except such symptomatic help as can be given and which may prolong life a few weeks or months.

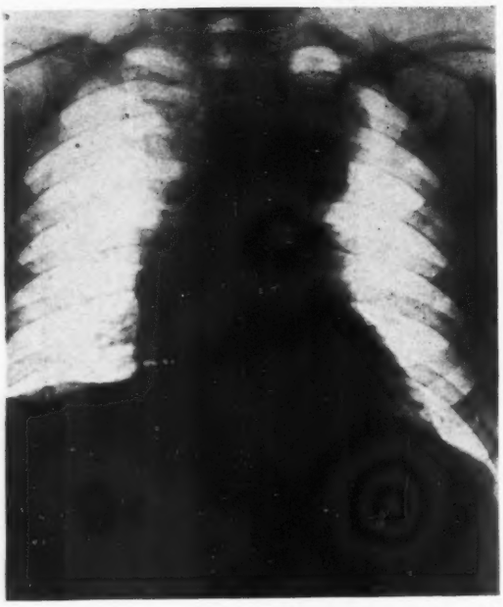

FIG. 3. Chest x-ray showing typical barrel-shaped aortic shadow with shadow of aneurysm extending through stomach air bubble.

CASE REPORT

This case shows the usual history of long-standing hypertension with enlarged heart. There was a beginning dissecting aneurysm two years earlier having some features of coronary occlusion and diagnosed as such in spite of a normal electrocardiogram.

He later suffered from a typical dissecting aneurysm in which the flow of blood in the dissected media could be traced clinically through its entire extent and then lived four months to die suddenly from rupture of the aneurysm into the left pleura and lung.

This male patient, age fifty-two, was first seen December 6, 1935, complaining of occipital headaches for six months. He had been under a severe nervous strain and worry for five years and had worked long hours.

Physical examination showed him to be markedly overweight, of ruddy florid complexion. The peripheral arteries felt somewhat sclerotic, and the heart was slightly enlarged to the left. All other physical findings, including ophthalmoscopic examination, were normal. The blood pressure was 230/130 in both arms taken while he was sitting up. The urine was normal except for many hyaline casts. The blood count was normal.

He was sent to the Presbyterian Hospital where renal function tests were normal, and blood chemistry was normal except for slightly elevated total non-protein nitrogen and uric acid. An electrocardiogram and x-ray film of the chest showed nothing but left axis deviation and slight enlargement of the left ventricle. He was kept in bed for several days. With sedatives and rest, his blood pressure dropped rapidly to 150/110. He was advised to shorten his hours of work, reduce his weight, avoid excitement, and was given small doses of phenobarbital and potassium iodide. The headaches disappeared, and the weight was reduced thirty pounds. The blood pressure averaged 150/116 for the next year. Beginning in January, 1937, he increased his hours of work and stopped his medicine, but continued relatively free from headaches until March, 1937.

First Small Perforation. While walking to the office after a heavy breakfast he was seized with a severe pain beneath the sternum, the pain being described as a pressure. He was taken home and seen an hour later. The pain was agonizing, requiring morphine, the pressure was 126/92, the pulse 112 with a regular rhythm, but the heart tones were indistinct and of tic-tac quality. There was no radiation to arms, neck or back. The patient was seen with Dr. James B. Herrick, who found dullness to the left of the spine from the fourth to the ninth thoracic vertebrae, and agreed that the probable diagnosis was a coronary thrombosis, in view of the history of pain, drop in blood pressure, and tachycardia. He was kept quiet for six weeks, then allowed a gradual increase of physical activity so that at the end of four months he was walking five miles daily; by this time the pressure had risen to about 180/100. The heart findings were again normal, and electrocardiograms taken every six months subsequently showed no remarkable change from the original tracing taken before the accident. (Fig. 1.)

His condition remained the same during the next two years except that he had two attacks of renal colic in April and November, 1938. He was seen every six months during that period for electrocardiogram and renal function tests.

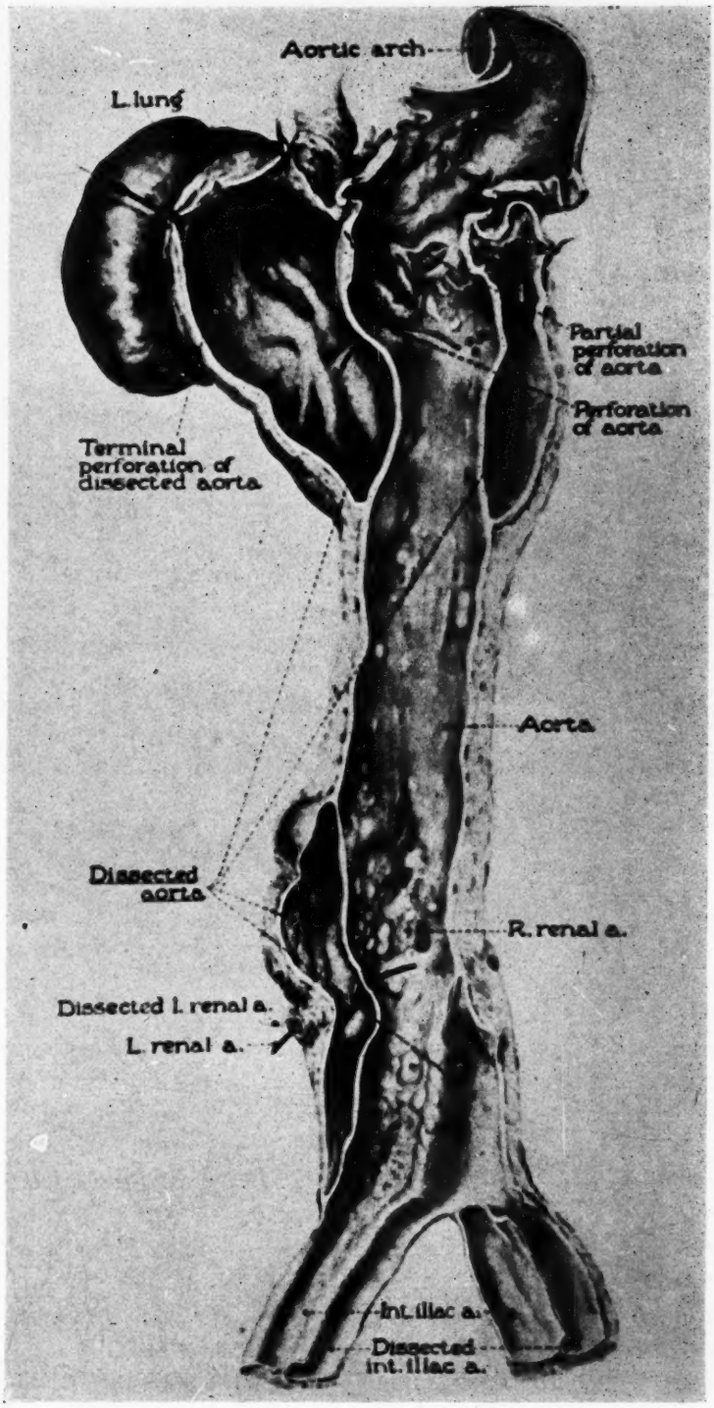

FIG. 4. Diagram drawing showing original healed partial perforation; second perforation which led to dissection; dissected aorta and its branches and terminal rupture of dissected aorta.

All of these were normal during this period except for the persistent hypertension of about 190/115, and a slight elevation of the uric acid and non-protein nitrogen content of the blood.

Onset of Second Dissection. On January 4, 1939, he was awakened at 1 A.M. with very severe pain beneath the mid-sternum going through to the back at the level of the angles of the scapulae directly in the mid line. Sometimes it would be worse in front and sometimes worse

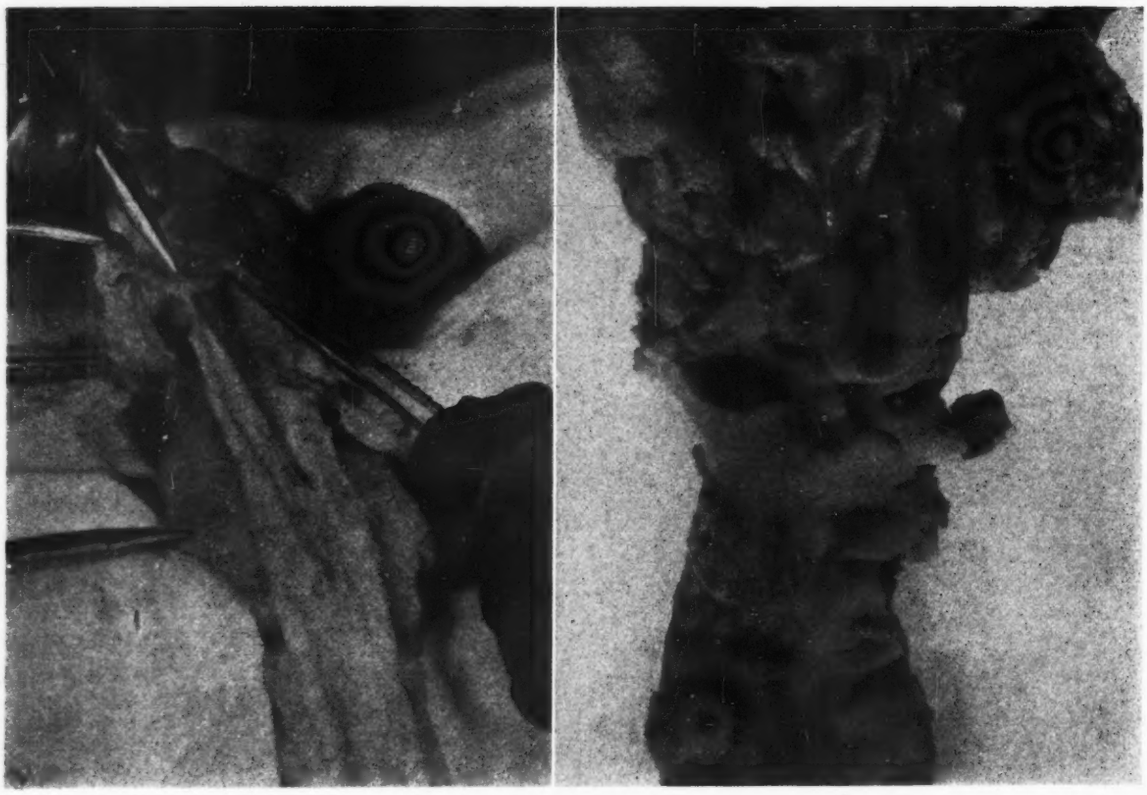

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FIG. 5. Photograph taken at autopsy showing the aorta to be composed of a tube within a tube.
FIG. 6. Root of aorta showing atherosclerosis; perforation through intima and its relation to aortic valve.

in the back. The pain was at all times excruciating, causing him to groan, to toss in bed and walk the floor. Sometimes it seemed to be pulsating or wave-like but did not subside at any time. He drank whiskey and hot water, and induced vomiting without relief. A physician was called and gave him a hypodermic of gr. ¼ of morphine at 3 A.M., 4 A.M. and 5 A.M. without the slightest relief, and then ordered four one quart enemas of soap suds and turpentine, all with no relief. He described the pain as entirely different in character and location from that experienced three years before, and from that of the attacks of renal colic in the past.

When seen by us at 3 P.M. he was groaning and writhing in pain. Temperature, pulse and respirations were normal. The trunk was warm, the extremities cold and clammy. The blood pressure was 230/116 in both arms. Examination was entirely normal except for slight cardiac enlargement to left and right, unchanged from previous examinations. There was also slight dullness in the back from the third to the sixth vertebrae on the left near the spine. By this time he stated that the substernal pain had lessened and the back pain was one or two inches lower.

He was brought to the Presbyterian Hospital in an ambulance with an admission diagnosis of dissecting aneurysm. The following additional findings were: red count and hemoglobin normal but the white blood count was 16,000. Urine was entirely normal. The cardiogram was unchanged from previous tracings except for slight inversion of T_3 and T_4. (Fig. 2.) A flat plate of the abdomen was normal. The blood pressure was 180/108.

He was seen by Dr. Herrick at 8 P.M. who confirmed the above and suggested a chest fluoroscopy and x-ray. These showed a pulsating area behind the heart extending from the aortic arch to about one inch above the diaphragm which pushed the lower esophagus forward and to the left.

Progress of Dissection. His clinical course was extremely stormy. The temperature rose rapidly

FIG. 7. Fatty medial plaque replacing muscle tissue.

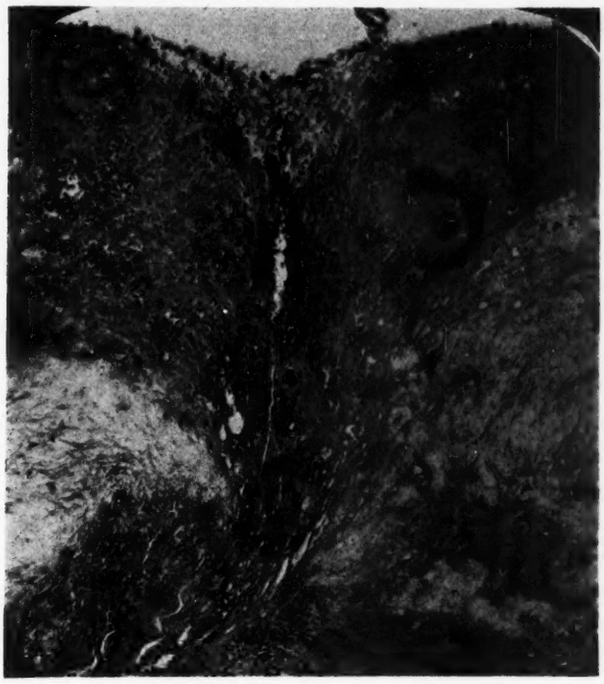

FIG. 8. Earlier original dissection into medial plaque with replacement by fibrous tissue and endothelialization of intima.

to between 101 and 103°F., where it remained until January 15th, the eleventh day of the disease. The pulse ranged from 100 to 120, and the respirations between 22 and 32 per minute. The blood pressure, however, remained elevated, at no time falling below 184 systolic and 96 diastolic. The pain was excruciating, necessitating very frequent injections of pantopon, an average of twelve injections daily for twelve days. In addition he was given large doses of bromide by rectum and by mouth.

At eleven o'clock the first night he began to hiccough. This continued with only brief remission for seven days in spite of everything that

could be done. On January 5th, an x-ray plate of the chest and abdomen showed a shadow extending through the diaphragm about half way through the stomach air bubble, suggesting, with the hiccough, that the aneurysm had become lower, being at about the level of the first and second lumbar vertebrae. (Fig. 3.) On January 6th and 7th the sclerae became yellow and the urine gave a positive test for bile. On the morning of the 7th he complained of pain in the epigastrium and that afternoon, pain in the region of the left kidney, the latter feeling "like the old kidney stones" except that it did not radiate downward to the groin and testis. This left lumbar pain recurred frequently during the next three days, (probably the time of the left renal artery dissection). By January 16th the abdominal pain had traveled down to the area between the navel and the symphysis pubis, and occasionally the feet were very cold. On January 24th it was noted in the record, "the last two days it has seemed possible to feel a slightly tender mass whose outline is very indefinite just to the left of the midline midway between navel and pubis. No definite pulsation is felt, but one wonders whether the dissection has extended to the bifurcation of the aorta."

By January 25th, the twenty-first day, the temperature and respiration had become normal and all pain had disappeared. By the first of February the pulse was in the seventies and remained so until February 11th, the thirty-ninth day in the hospital, when he returned to his home. He remained quiet there for ten days and then went to Florida, it being felt that since the prognosis was most grave, he would be happier there. His physical activity was greatly limited, but he took short automobile rides and was contented and entirely free of symptoms.

Final Rupture into Pericardium. On April 29th, 115 days after the original accident, after eating a large dinner, he rose from the table, walked about ten steps, clutched his chest, regurgitated a little bright red blood, and died within a minute of the onset of pain. The autopsy was done by Dr. Robinson, of Fort Lauderdale, and the heart and aorta sent to Chicago for further examination. (Fig. 4.)

The essential findings in the autopsy as performed by Dr. Robinson, "The heart was of normal size. The ascending and transverse arch of the aorta was moderately dilated as were the great vessels arising from the arch, to a less degree. Just distal to the left subclavian artery the antero-medial surface of the aorta was adherent to the pleura of the left upper lobe of the lung. In this area there was a tear in the wall of the aorta, measuring about 5 mm. in diameter. The tear was irregular in outline, and no evidence of clot formation was present on the margins. The aortic wall at this point was less than 1 mm. in thickness and was deep purplish red in color over an area of 2 cm. in diameter. The ecchymotic area was very friable. There was also a slit 2 cm. wide and 1.5 cm. deep in the arch of the aorta completely endothelialized. On opening the abdominal aorta it was found that the aorta consisted of a tube within a tube. (Fig. 5.) The external tube had a wall consisting of fibrous tissue and was approximately 2 mm. in thickness. The internal surface of the outer tube and the external surface of the inner tube were covered with a smooth shining surface. In several places there were antemortem thrombi adherent to the inner surface of the external tube. The inner tube was the aorta, and the two tubes were in contact and their walls merged over only a narrow area. The circumference of the aorta and its caliber were diminished by about 30 per cent. (Fig. 6.) The endocardial surface of the aorta showed a moderate atherosclerosis. The above condition extended as far distally as was dissected, that is, into the internal and external iliac arteries.

The posterior surface of the left upper lobe of the lungs were adherent to the aorta at the site of the rupture. The apex of the left upper lobe was firm, non-crepitant and deep purplish red in color. This area cut with increased resistance and the cut surface bled fully. The remainder of the lungs were normal."

Microscopic examination of the tissues was done by Dr. Apfelbach at the Presbyterian Hospital.

Microscopic sections of the aorta revealed multiple medial plaques in which the muscle was replaced with fat, often somewhat caseous, and fibrous tissue. The earlier beginning dissection was seen to have healed over with fibrous

tissue. The wall being lined with regenerated endothelium. (Figs. 7 and 8.)

The coronary arteries and the myocardium were normal.

COMMENTS

A case of dissecting aortic aneurysm has been presented in which it was possible to trace the dissection through the various branches of the aorta. This patient had had an earlier beginning dissection which at the time was thought to be a somewhat unusual coronary occlusion.

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Acute Thrombocytopenic Purpura Complicating Rubella*

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THROMBOCYTOPENIC purpura is an unusual, but not rare, complication of many acute infections;[8,10,13,14,15] however, it has seldom been described as being associated with rubella. In the past few years interest in German measles has been stimulated by the high incidence in the armed forces and because of the large epidemic in Australia.

During the winter season of 1945 to 1946, at the Regional Station Hospital, Fort Bragg, North Carolina, we have observed two cases of thrombocytopenic purpura associated with rubella which are worthy of report in order to emphasize the occurrence of this complication. The blood picture of a small group of eleven consecutive patients with this disease has been studied in order to determine if there is a depression of platelets in the peripheral blood of these patients and the findings are recorded and discussed.

CASE REPORTS

CASE 1. A twenty-two year old, white soldier (W. B.) was admitted on February 6, 1946, because of fever, slight malaise and a rash on his face, neck and body of eight hours' duration. There were no symptoms of an acute upper respiratory infection. No drugs had been taken.

The physical examination on admission revealed a soldier in no acute distress with a temperature of 100.2°F., a pulse rate of 100 per minute, respiratory rate of 22 per minute. There was a fine, pink maculopapular rash over the face, neck and trunk. Marked occipital and postauricular lymphadenopathy was present. There were no Koplik spots seen. The laboratory studies of the peripheral blood and urine were within normal limits.

No drugs were administered. The rash began to fade rapidly and the temperature returned to normal the day following admission. On February 8th, the rash had entirely disappeared and the patient was asymptomatic. A spontaneous epistaxis occurred on the evening of February 9th, and it was found to be very difficult to stop by the usual methods. The following day bleeding from the nose recurred and at that time many purpuric lesions averaging 2 to 3 mm. were seen over the entire body and extremities. Further examination revealed spongy, bleeding gums. A tourniquet test was markedly positive. Laboratory investigation showed the platelet count to be 4,000 per cu. mm.; red blood count of 4,800,000 per cu. mm.; a hemoglobin of 90 per cent (Newcomer) and a normal white blood cell count and differential. In determining the bleeding time it became necessary to apply pressure over the puncture wound after thirty minutes, due to the profuse bleeding; oozing from this wound still occurred twenty-four hours later. The clotting time was four and one-half minutes and the venous blood clot did not retract at all in twenty-four hours. The prothrombin time was normal.

A blood transfusion of 500 cc. of fresh, whole blood was given without reaction. There was no elevation of the blood platelets noted following this transfusion. Large doses of vitamin C were given parenterally each day.

The patient continued to have marked bleeding from his gums as well as severe nose bleeds which were not successfully controlled by nasal packs with ephedrine. Hemostatic globulin was used on nasal packs commencing February 12th,

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with apparent benefit. There were no further nose bleeds but minimal bleeding from the gums continued until February 14th, at which time the mucous membranes began to appear healthier. A blood transfusion of 500 cc. was given on February 17th because of the patient's anemia and clinical weakness. The patient

minute and the respirations were 20 per minute. A generalized, red, morbilliform rash was noted on the face and body. The posterior cervical and occipital lymph nodes were markedly enlarged. Koplik spots were not present. The laboratory studies of the peripheral blood and the urine were normal on admission.

TABLE I

LABORATORY DETERMINATIONS IN TWO CASES OF THROMBOCYTOPENIA PURPURA

Case	Date	Platelets per Cu. Mm.	Bleeding Time	Clotting Time	Red Blood Cells	Hemoglobin (Newcomer) Per Cent	Tourniquet Test
I	February 10	4,000	30 minutes*	4½ minutes	4,800,000	90	++++
	February 11	14,000	.....	.....	4,300,000	90	
	February 12	18,000	.....	.....	3,950,000	80	++++
	February 13	10,000	.....	.....	3,850,000	80	
	February 14	21,000	.....	.....	2,820,000	51	
	February 15	13,000	.....	.....	3,500,000	59	
	February 16	86,000	.....	.....	3,900,000	70	++
	February 19	132,000	12 minutes	4½ minutes	4,260,000	80	
	February 20	122,000					
	February 21	118,000	.....	.....	3,920,000	80	
	February 23	120,000	.....	.....	4,650,000	90	
	February 25	132,000	.....	.....	4,820,000	95	
	March 4	184,000	.....	.....	4,480,000	90	
	March 8	290,000	3½ minutes	4 minutes	4,570,000	95	Negative
II	March 25	80,000	11 minutes	4½ minutes	4,560,000	90	++
	March 26	126,000					
	March 27	127,000	.....	.....	4,180,000	80	
	March 30	210,000	4 minutes	4½ minutes	4,840,000	90	Negative

* Pressure applied after thirty minutes due to profuse bleeding. Oozing from puncture wound still taking place twenty-four hours later.

gradually improved; the purpura had entirely disappeared by February 20th, and the gums appeared normal at that time also. The soldier was returned to full duty on March 11th. The laboratory findings were normal on discharge. (Table I.)

CASE II. This eighteen year old, white soldier (H. O.), was admitted to the communicable disease ward of The Regional Station Hospital on March 23, 1946, complaining of fever, malaise and a rash over his face and body of twenty-four hours' duration. There were no symptoms of an acute respiratory infection. No drugs had been taken.

The physical examination at that time revealed a well developed, well nourished, white male who did not appear to be acutely ill. The temperature was 102.8°F., pulse was 92 per

The patient rapidly became asymptomatic and his rash began to fade on the second hospital day. No drugs were administered. Three days following admission many small purpuric lesions averaging 1 mm. in diameter were noted over his entire body. At this time, he was found to have a markedly positive tourniquet test, a platelet count of 80,000 per cu. mm., bleeding time of 11 minutes, clotting time of 4½ minutes and poor clot retraction at 24 hours. The patient showed no evidence of spongy gums, epistaxis or other bleeding tendencies. At this time he was afebrile and the temperature did not become elevated during the remainder of his hospital stay. The following day the platelet count was 26,000 per cu. mm.; the daily changes are noted in Table I. By March 29th, the purpuric rash had faded markedly and only minute

areas of pigmentation remained. On March 31st, the patient showed no further evidence of a rash, he was asymptomatic and returned to full duty on the following day.

PLATELET COUNTS IN ROUTINE CASES OF RUBELLA

Material. Eleven consecutive patients with rubella were carefully studied by means of platelet counts, red blood cell and white blood cell determinations and tourniquet tests. Bleeding and clotting times were performed on patients having lowered platelet counts.

Methods. Platelet counts were done by the direct Thorndike method. The bleeding time was determined by means of the Duke method and the coagulation time by the use of glass capillary tubes. The tourniquet tests were performed by counting the number of petechiae in an area 2.5 cm. square and 4 cm. below the antecubital fossa after leaving the blood pressure cuff inflated for fifteen minutes mid-way between the patients' systolic and diastolic blood pressures. Normally no more than ten spots should appear five minutes after the pressure is released.

Results. In three instances the number of platelets in the peripheral blood was definitely diminished and in one (Case III) the diminution was marked. (Table II.) This patient also showed a markedly positive tourniquet test, this being the only one positive in the entire series. The bleeding time in this patient was 6 minutes and the clotting time 2¼ minutes when the thrombocytes were at the lowest point. After the number of platelets had returned to normal the tourniquet test was negative and the bleeding time was 3½ minutes.

TABLE II
PLATELET COUNTS AND TOURNIQUET TESTS ON ELEVEN CONSECUTIVE CASES OF RUBELLA

Case	Platelet Counts			Tourniquet Test on Admission
	Admission	Third Hospital Day	Sixth Hospital Day	
I	278,000	249,000	250,000	Negative
II	250,000	272,000	.....	Negative
III	88,000	204,000	250,000	Markedly positive
IV	198,000	260,000	250,000	Negative
V	334,000	300,000	.....	Negative
VI	123,000	.....	193,000	Negative
VII	311,000	302,000	.....	Negative
VIII	265,000	248,000	250,000	Negative
IX	311,000	320,000	309,000	Negative
X	131,000	.....	220,000	Negative
XI	351,000	307,000	301,000	Negative

COMMENTS

Dunlap in 1871,[3] described a case of purpura associated with German measles. This was soon followed by similar reports by Cheadle,[2] Erskine[4] and Glaister.[5] These authors all described instances of purpura having its onset soon after the fading of the rubella rash, but the description of the laboratory findings was meager. Pitten[13] and Gunn[6] each reported an instance of rubella complicated by thrombocytopenic purpura of a mild degree, manifesting the typical blood findings of thrombocytopenia, prolonged bleeding time, normal clotting time and diminished clot retraction. Warren et al.,[17] reported two cases demonstrating both renal and intestinal bleeding, in addition to purpura, epistaxis and gingival bleeding.

Thrombocytopenic purpura has been associated with measles more commonly than with rubella[8,10,14,16] and similarly with many other acute infections, such as varicella,[15] infectious mononucleosis,[7,14] acute upper respiratory infections,[8] lobar pneumonia[8] and acute sinusitis.[8]

Olef[9] has demonstrated by a careful study that thrombocytopenia may occur during the initial stage of many acute infections. It therefore seems reasonably clear that the thrombocytopenia occasionally associated with rubella may be regarded as an example of this non-specific reaction.

The exact mechanism of the occurrence of this phenomenon is unknown but it is believed to take place in one of several ways. Olef[9] attributed the thrombocytopenia in acute infections to the clumping of the platelets around the invading organisms as a means of overcoming infection by the body. McLean et al.,[8] reported purpura occurring six to nineteen days after the onset of the acute infection and suggest the possibility that the thrombocytopenia may be an allergic manifestation particularly affecting the megakaryocytes in the bone marrow. Patek[10] likewise is of the opinion that the decreased number of platelets in the peripheral blood may be the result of an allergic or hypersensitive state. The production of thrombocytopenia in acute infections may be a manifestation secondary to increased capillary permeability in which the platelets are diminished in number, helping to reinforce the weakened vessel walls.[10,11,16]

It seems reasonable to assume that the thrombocytopenia may be brought about by a direct depression of platelet formation in the bone marrow by the infectious agent, the megakaryocytes being normal in number.[16] Purpura may then occur due to a combination of the lack of platelets to plug defects in the walls of injured capillaries and the increased bleeding time.

The treatment of thrombocytopenic purpura complicating an acute infection should be one of conservatism. Complete bed rest is essential. Measures should be taken to stop bleeding from the nose. Hemostatic globulin used on nasal packs appeared to be effective in stopping the epistaxis in Case I. Bleeding gums will rarely be of sufficient severity to cause great concern. Hemorrhage from the urinary or gastrointestinal tract is much more difficult to manage and usually all efforts are useless until a spontaneous remission occurs. Transfusions are of value if the blood loss is sufficient to necessitate them; they are of no value in either increasing the platelet count or diminishing the bleeding time. Ascorbic acid may be of value because of the increased capillary fragility, but there is no evidence to make one believe that vitamin K is beneficial. Splenectomy is unnecessary in most instances and it is doubtful if such a procedure is ever justified in thrombocytopenic purpura resulting as a complication of an acute infection. This operation, at least, should certainly be reserved for those patients having fulminating, uncontrollable hemorrhages.

SUMMARY

1. Two cases of thrombocytopenic purpura complicating rubella are reported. In Case I the purpura was noted the third day after the onset of the illness and about thirty-six hours after the disappearance of the rash of German measles. In Case II the purpura appeared on the fourth day of illness and at a time when the primary rash had almost completely disappeared.

2. Platelet counts and tourniquet tests were performed on eleven consecutive patients with rubella, three of whom revealed an initial lowering of the platelets. One of these patients had a moderate thrombocytopenia, a markedly positive tourniquet test and a prolonged bleeding time.

3. The theoretical mechanisms of this phenomenon were discussed.

4. The treatment of thrombocytopenic purpura complicating acute infections should be directed toward controlling the hemorrhages and treating the resulting anemia. Recovery occurs spontaneously within a few days in most instances, and splenectomy is probably never necessary.

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Fulminating Meningococcemia with Gangrene*

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SINCE the publication of Herrick's classical report,[1] an increasing amount of attention has been paid to the bacteremic features of infection with Neisseria intracellularis.[2] It is now generally believed that in 10 to 35 per cent of systemic invasions by this organism, the meninges are not involved at the time the initial diagnosis is made. The higher incidence of bacteremia without meningitis probably represents only the fact that in more cases the diagnosis is being made earlier. Acute, subacute or chronic forms of meningococcic septicemia have been described, ranging in severity from a mild and relatively innocuous disease to a fulminating and highly fatal one. The latter type, often referred to as the Waterhouse-Friderichsen syndrome, is usually so rapidly fatal that relatively few clinically demonstrable complications have been recorded. However, with the advent of such specific therapeutic agents as the sulfonamide drugs and penicillin, more patients are surviving, even though they may have had infections of an extremely malignant type. Consequently, some cardiovascular complications are being observed.

It is the purpose of this paper to report a case of fulminating meningococcemia with gangrene of the lower extremities. This complication appears to be something of a rarity; at least, it is not described in recent reports[3–6] of large groups of cases recorded from army training camps. Herrick mentioned one case, but did not give any details; Bernstein[7] reported a case of meningococcic meningitis with peripheral gangrene, and Hayes and Whalen[8] also reported a case in which most of the characteristics of the Waterhouse-Friderichsen syndrome were presented, with bilateral gangrene of the toes and multiple zones of cutaneous gangrene. Their patient recovered, as did Bernstein's and ours, after treatment with penicillin and sulfonamide drugs.

CASE REPORT

An eighteen year old seaman was admitted to a naval hospital on November 13, 1945, in a disoriented condition, with a temperature of 100°F. (37.7°C.). On admission, he complained principally of chills, sore throat, headache, and extremely painful legs and toes. He had suddenly been prostrated by a severe chill the evening before while at work, and at that time had noticed severe pain in his feet. Results of physical examination were essentially negative, except for extensive purpuric and ecchymotic lesions over the dorsa of his hands and over the dorsal and plantar surfaces of both feet; a few scattered purpura were seen on other areas of his body. The feet were cold, blue and hypersensitive, and there was unmistakable evidence of interference with arterial circulation. There was neither evidence of meningeal irritation nor signs of shock or vascular collapse; the blood pressure remained consistently within normal limits.

A diagnosis of acute meningococcemia was made. The patient was immediately given an initial dose of 4 Gm. of sulfadiazine; thereafter,

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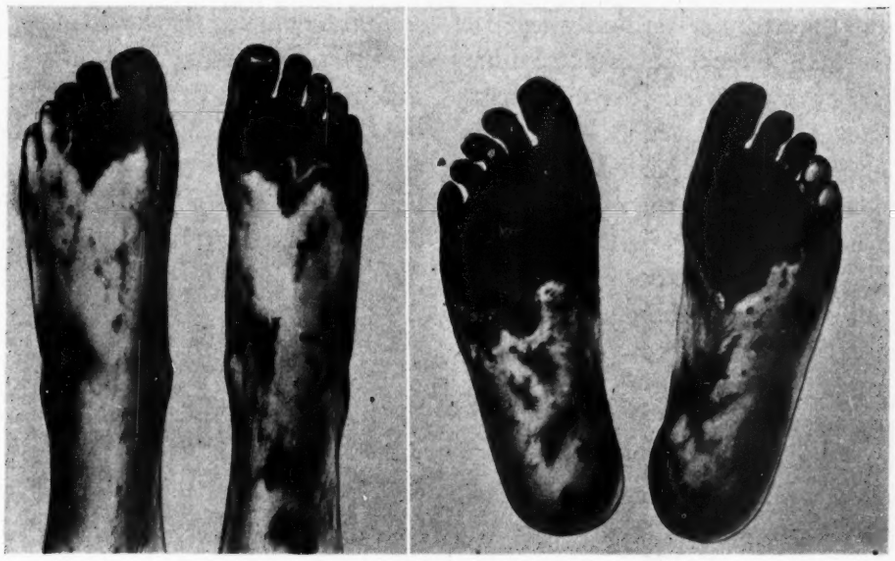
he received 1 Gm. every four hours. Subsequently, a dose of 30,000 units of penicillin was ordered to be administered intramuscularly every two hours.*

Lumbar puncture revealed that the cerebrospinal fluid was clear and colorless and that the pressure was 240 mm. of water. The number of cells and protein content were normal. Leukocytes numbered 28,000 per cu. mm. of blood. The erythrocyte count and results of the Kahn test were normal. The sedimentation rate of erythrocytes was 30 mm. in one hour (modified Cutler method). Culture of material from the throat produced Neisseria intracellularis. Culture of specimens of blood and material from blebs produced the same organism, type II A. The organism exhibited complete sensitivity to 0.5 units of penicillin per cc. of culture medium. Results of laboratory procedures including the prothrombin time, bleeding time, clotting time, icterus index, determination of blood urea nitrogen, and urinalysis were all within the range of normal. A roentgenogram of the thorax showed no abnormalities.

The subsequent clinical course of this patient, although generally satisfactory, revealed that the infection was somewhat refractory to treatment. The patient continued to have daily elevations of temperature, in spite of the use of increased doses of penicillin administered intravenously and continued sulfadiazine therapy. The administration of sulfadiazine was temporarily discontinued on the sixth hospital day in the belief that it might have been the cause of the continued pyrexia. The administration of penicillin was continued in the interval. This procedure proved to have no effect on the temperature curve. On November 16th (three days after admission of this patient), results of a routine electrocardiogram were within normal limits and those of examination of the heart were objectively negative. Three days later, gallop rhythm developed, and a blowing systolic murmur was heard at the apex cordis, with decreased intensity of both the first and second sounds. At the base, the murmur was greatly diminished in intensity and the pulmonic second sound was accentuated. This was tentatively interpreted as evidence of acute myocarditis and possibly of acute endocarditis. Results of the electrocardiogram remained normal, however, and by November 20th the gallop rhythm had disappeared and the systolic murmur was greatly diminished in intensity. Between November 26th and December 2nd, the patient was afebrile. On November 30th, the use of all specific medications was discontinued. On December 2nd, the fever returned and on December 6th, the temperature reached 102°F. (38.8°C.). The administration of both penicillin and sulfadiazine was resumed and the patient became afebrile on December 10th. Results of culture of specimens of blood were negative during this episode, and no new purpuric lesions appeared.

The circulation of the patient's feet continued to show evidence of inadequacy, which seemed to increase rather than decrease. Moderate edema developed in both feet, and the ecchymotic lesions of the feet and toes persisted. Pulsations of the posterior tibial arteries remained normal, but pulsations of the dorsalis pedis artery could not be felt in either foot. No new areas of ecchymosis appeared, but edema, bluish discoloration and coldness persisted and a red line of demarcation gradually made its appearance. (Fig. 1.) At no time was there objective evidence of peripheral neuritis or of caudal myelitis, conditions which have been described as complications of meningococcic infections. By November 21, 1945, the distal portion of the right great toe and the great second and third toes on the left foot had become definitely gangrenous. Block of the periarterial sympathetic fibers with procaine hydrochloride was attempted at one time, in the hope that this would arrest the gangrenous process, but the procedure proved to be of no avail. The gangrenous parts were kept at complete rest under a heat cradle, with frequent changes of warm moist antiseptic packs. Although low-grade fever persisted, with occasional increases in temperature after December 10th, the general condition of the patient gradually improved. On December 19, 1945, all

* Since this article was submitted for publication we have found three additional references to patients with meningococcemia and gangrene, one in 1917 and two recent ones in 1946 and 1947. In the two latter subjects there was extensive gangrene requiring amputation of the lower extremities. One patient required skin grafting for areas of cutaneous gangrene while the other lost portions of his fingers. This brings the total number of such patients now on record to seven. References are appended on the bibliography (12, 13 and 14).



A B

FIG. 1. A, appearance of patient's ankles; B, plantar surfaces during the third week of illness, showing gangrene and ecchymotic regions. (Official United States Navy drawing, courtesy United States Naval Hospital, Oakland, California.)

gangrenous toes were removed surgically. The patient improved rapidly thereafter and, after plastic repair of the distal portions of the feet, he was dismissed in good general health, with only minor impairment of his gait.

COMMENT

Although acute meningococcemia frequently may be explosive in onset, at times it is characterized by a paucity of symptoms and a relatively mild course unless meningeal involvement occurs. An erythematous or purpuric rash, myalgia, arthralgia, fever and chilling usually are present, and there may also be nausea and vomiting, headache and sore throat. The spleen is sometimes palpable. In many cases a subacute form of the disease superficially resembles acute rheumatic fever. When the disease is milder, the prognosis is not unfavorable, barring the appearance of endocarditis or meningitis. In some cases recovery without medication has occurred; three such cases in which the patients were children have been reported by Silverthorne.[9]

It is of interest that in Bernstein's case, in Hayes and Whalen's case, and in the case we have reported, evidence of definite vascular occlusion involving the toes appeared within the first twenty-four hours after the onset of symptoms. Our patient complained of cold, painful feet and toes as an initial symptom, and although the pain subsequently diminished, the interference with circulation persisted and was of sufficient magnitude to lead to gangrene. In Bernstein's case, causalgia involving one arm was a prominent and prolonged feature; but arterial involvement of the arm was not noticed.

Although the cause of gangrene in meningococcic septicemia has not been definitely established, Bernstein has postulated that it is a trophic disturbance based on a common, widespread, vascular lesion, embolic or autochthonous, or on a peripheral vasospasm caused by a toxin produced by the invading organism. It is not difficult to believe that the symmetric lesions in our case could have been caused by bacterial emboli involving the distal distribution of the dorsalis pedis arteries.

In our case, there was no good reason to consider the possibility of an associated endocarditis. Although meningococcic myocarditis, associated with endocarditis, has been recorded in a small number of cases,[10]

a search of the literature reveals only seventeen cases of meningococcic endocarditis and twelve of myocardial involvement, usually with fatal termination. Holman and Angevine[4] recently have reported two such cases of myocarditis; in one the myocarditis was proved at necropsy and in the other it was disclosed by serial electrocardiograms. In our case, myocarditis and bacterial endocarditis were at one time suspected, although never definitely proved. Once treatment had been instituted, results of all subsequent cultures of specimens of blood were negative, and signs and symptoms referable to the heart rapidly disappeared.

Among the three types of Neisseria intracellularis, types I, II and II A, there has been reported no appreciable variance of virulence; there has been, however, evidence that strains of type II may be found more commonly in the presence of endemic meningococcic septicemia, whereas strains of type I predominate during epidemics of the disease (Thomas).[3] At times, no organism can be demonstrated during life, even when fulminating meningococcemia is present. Martland,[11] in a series of nineteen such cases, reported that the meningococcus was recovered from the blood in only two; many of his patients were found dead or died soon after admission to hospital, however, and the diagnosis was made at necropsy. Neisseria intracellularis, type I, is by far the most prevalent organism in acute meningococcemia; it occurs in about 90 per cent of cases. Type II A is present in 8 per cent of cases, and type II is the offending organism in less than 3 per cent. As has been stated, Neisseria intracellularis, type II A, was recovered from our patient by culture of both specimens of blood and material from blebs. In spite of observed sensitivity to penicillin in vitro, the organism appeared to be resistant to treatment, as shown by the prolonged illness and persistently febrile course of the patient.

This case suggests that more attention should be paid to the status of the peripheral vessels of patients who have fulminating meningococcic sepsis and, furthermore, that the possibility of the presence of embolic or vasospastic lesions elsewhere in the body deserves serious consideration in all cases of this type.

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Salicylates in the Prevention of Erythroblastosis Fetalis*

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A RECENT editorial in The Journal of the American Medical Association[1] suggested that Homburger's study[2] of the ability of sodium salicylate to inhibit anti-Rh immunization in animals "may in time result in the development of a practical method for the prevention of erythroblastosis fetalis." While Homburger did not suggest salicylate prophylaxis for erythroblastosis fetalis in man because of the known toxicity of salicylates, the previous experience of one of us[3,4] indicated that this should be a safe procedure if plasma salicylate levels did not exceed 400 to 500 micrograms per cc. Since the appearance of a suitable patient coincided with the publication of the above mentioned editorial, we proceeded with a trial of salicylate prophylaxis.

CASE REPORT

Mrs. M. D., a thirty year old nurse, para 1, gravida 3, had a severe blood transfusion reaction following a thoracic operation in May, 1942, and a second severe reaction in July, 1943, following a transfusion given at the time of a spontaneous abortion. She promptly became pregnant again and at an army hospital was delivered at term in May, 1944, of a stillborn, hydropic, female infant weighing 3,350 Gm. The patient claimed that an autopsy on this infant showed lesions characteristic of erythroblastosis. Postpartum, it was determined that the patient was Rh negative and her husband Rh positive. Despite the use of a vaginal occlusive diaphragm the patient became pregnant again and presented herself for management in June, 1946. The last menstrual period had begun on March 6, 1946. The physical examination revealed a slender, white female weighing 111 pounds, height 62 inches, blood pressure 125/70, with uterine enlargement corresponding to a gestation of fourteen to fifteen weeks' duration. Blood samples from both patient and husband gave the following reactions:

Patient: Group A, MN, Rh negative, Hr′ positive
No agglutinating Rh antibodies
Blocking antibody titer 1:8
Husband: Group A, MN, Rh_2, Hr′ positive

It was not possible to determine whether the husband was homozygous or heterozygous with respect to the Rh factor,[5] since no Hr″ serum was available for determination of genotype.

On June 17, 1946, the patient was started on a course of sodium salicylate, 8 Gm. daily in four doses and this was subsequently increased to 10 Gm. daily. The medication was continued for a period of twenty weeks or until delivery on November 7, 1946. Because of minor symptoms of salicylate intoxication the patient did not take the prescribed dosage regularly. Plasma salicylate levels (method of Brodie et al.,[6]) and Rh antibody titers during therapy were as shown in the table on page 662.

At no time were any agglutinating antibodies found in the maternal blood. Although the fall in blocking antibody titer starting the twenty-fourth week of pregnancy might have suggested that salicylates were interfering with antibody production, the outcome indicated a therapeutic failure. Fetal movements ceased on November 6th, in the thirty-fifth week of gestation and a macerated, stillborn, female infant weighing

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† Present address San Francisco, Calif.

2,440 Gm. was delivered on November 7, 1946, after a labor of six hours. Autopsy on the infant confirmed the suspicion of erythroblastosis fetalis, with characteristic findings in the liver, spleen, lungs, brain and placenta. The salicylate level in serous fluid from the fetal abdomen was

Date	Salicylate Level (micrograms per cc.)	Blocking Antibody Titer (against Rh_0 Cells)
6/28/46	201	1:32
7/1/46	222	
7/10/46	200	1:128
7/15/46	220	1:128
7/26/46	...	1:256
8/5/46	201	
8/16/46	246	1:4096
8/26/46	186	1:128
9/9/46	319	1:8
9/17/46	274	1:4
9/26/46	170	1:2
10/2/46	325	1:1
10/9/46	187	1:8
10/17/46	164	1:1
10/25/46	293	0
11/4/46	250	0

174 micrograms per cc. No blood could be obtained from the fetus, although cardiac puncture was attempted at the moment of birth. The mother made an uneventful recovery and was discharged on the fifth postpartum day. Thirty hours after delivery there were no Rh antibodies in the maternal serum, but on the tenth postpartum day blocking antibodies were present in a titer of 1:4 and a month later the titer was 1:32.

CONCLUSIONS

While the results of salicylate prophylaxis in this instance were disappointing we would not suggest the procedure be abandoned. Despite the difficulties of salicylate therapy we believe that it should be given further trial, beginning earlier in pregnancy and attempting to maintain higher blood levels of salicylate than were obtained in this patient. Certainly no other "rational" measure can be offered at present to the sensitized Rh negative mother who is eager to bear a normal child, unless the use of Rh haptens as suggested by Calvin, Evans, et al.[7] can be made clinically applicable.

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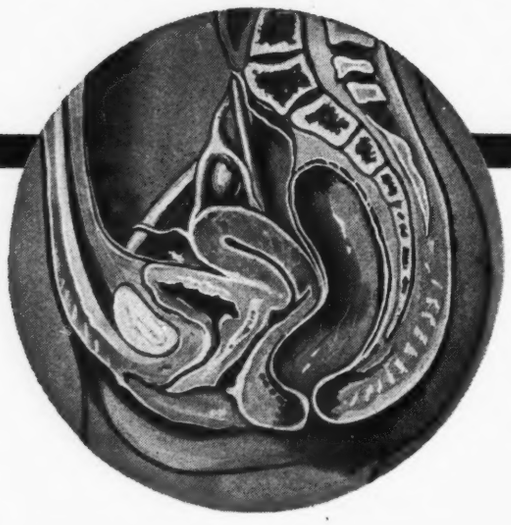

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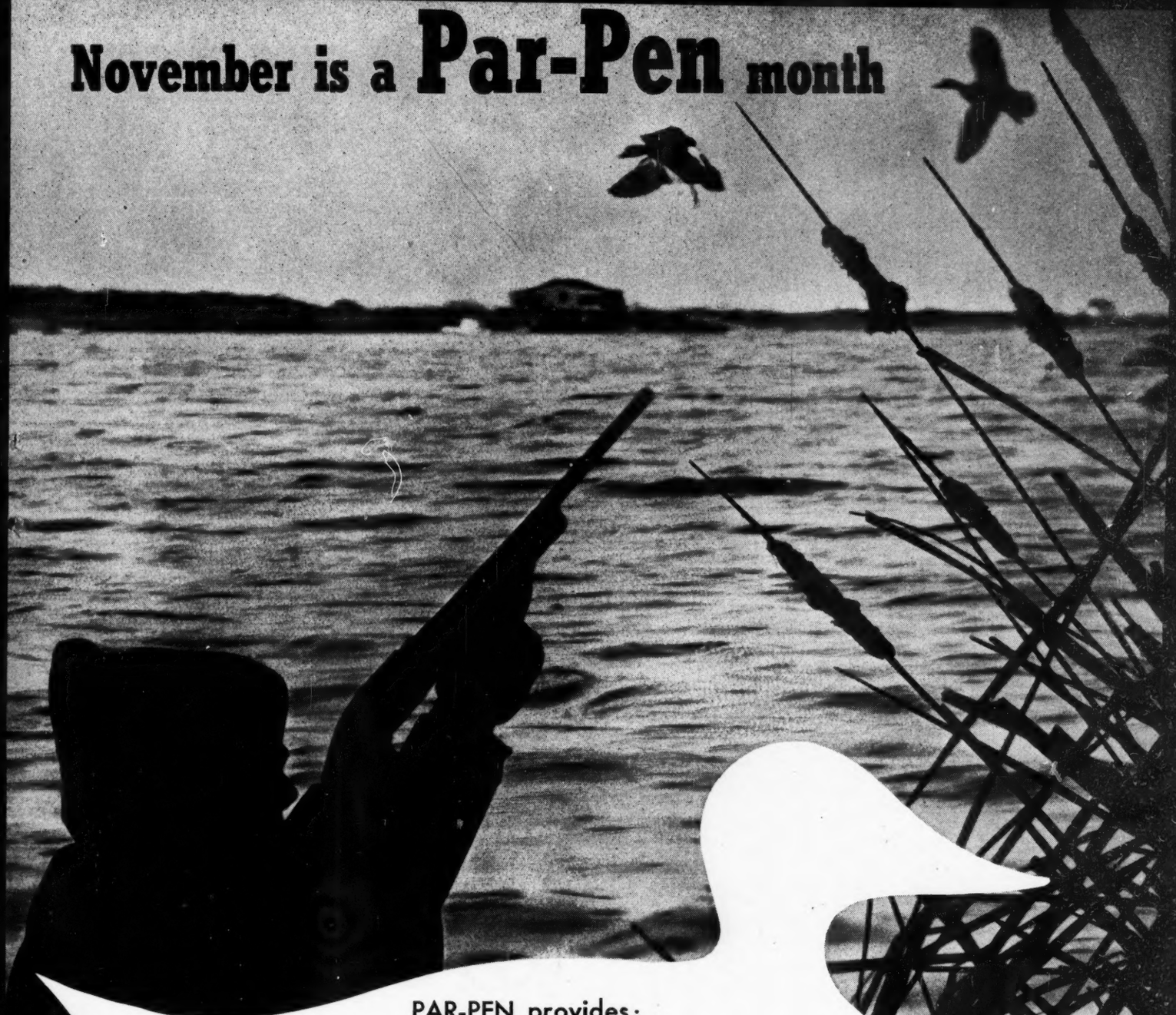

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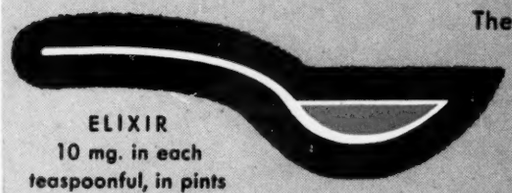

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ECZEMA	128	79	7	42	61.7
HAY FEVER	425	350	36	39	82.4
ASTHMA	435	275	7	153	63.2
MIGRAINE	73	48	1	24	65.7
ANGIONEUROTIC EDEMA	54	46	1	7	85.2
ATOPIC DERMATITIS	66	42	1	23	63.6
PRURITUS	24	18		6	75.0
ERYTHEMA MULTIFORME	28	22		8	78.6
DERMOGRAPHIA	20	15		5	75.0
FOOD ALLERGY	37	32		5	86.5
CONTACT DERMATITIS	63	49		14	77.7
PHYSICAL ALLERGY	11	7		4	63.6
REACTIONS—ANTIBIOTIC	84	81	1	2	96.4
REACTIONS—DRUGS	46	42		4	91.3
REACTIONS—BIOLOGICS	12	12			100.0
DYSMENORRHEA*	44	38		6	86.3
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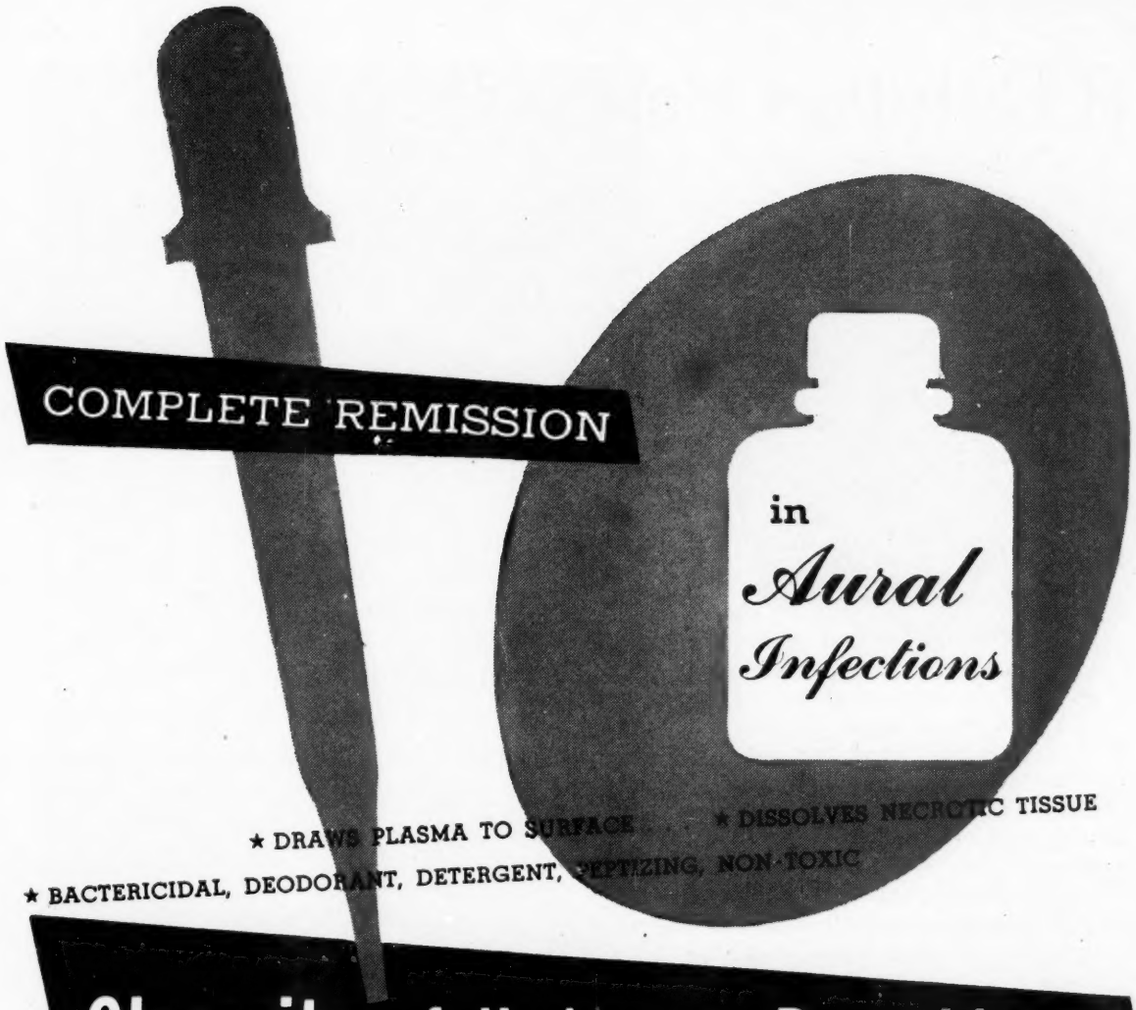

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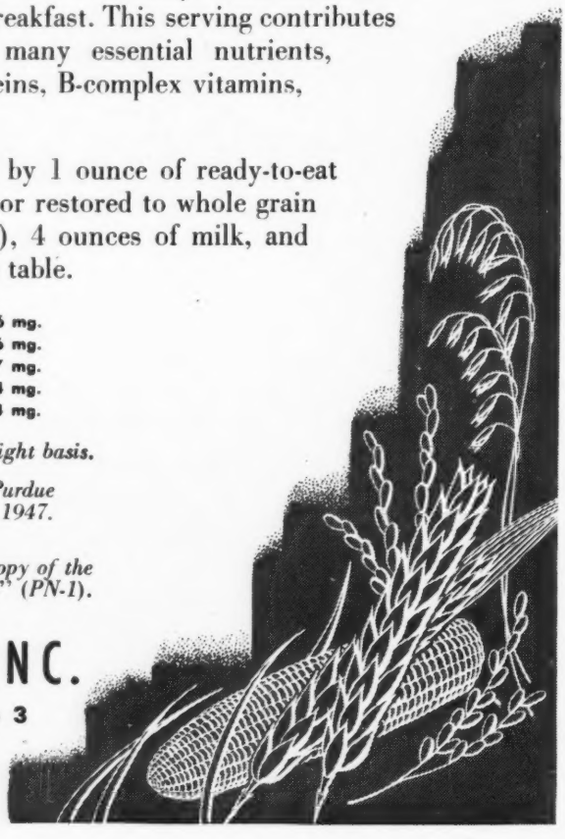

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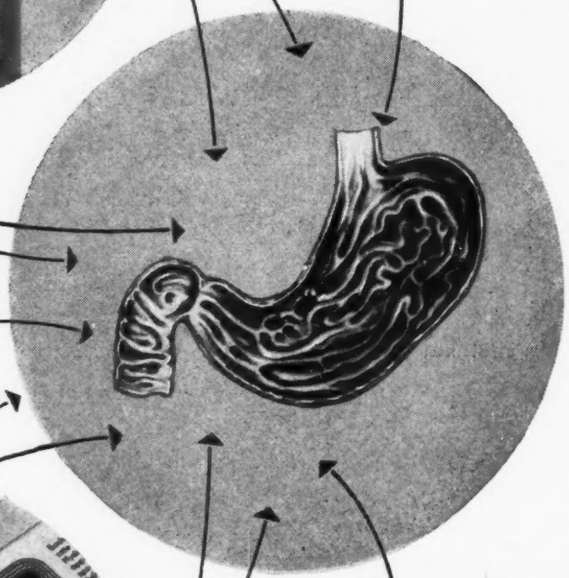

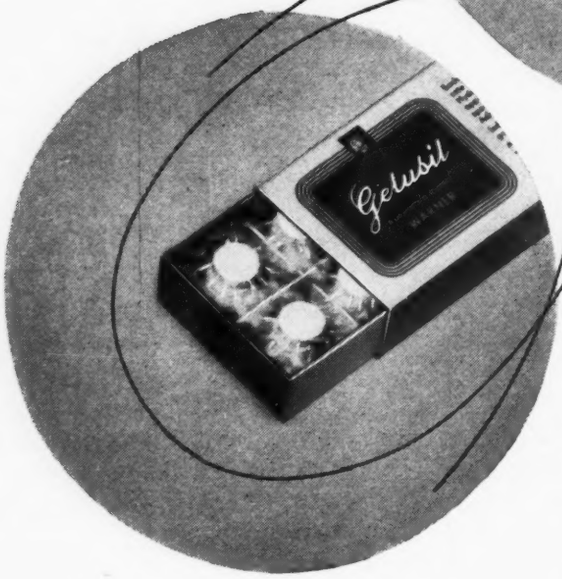

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